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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 26

[EPA-HQ-OPP-2010-0785; FRL-9353-4]

RIN 2070-AJ76

Protections for Subjects in Human Research Involving Pesticides

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: EPA is finalizing narrowly tailored amendments to the portions of its rules for the protection of human subjects of research applying to third parties who conduct or support research with pesticides involving intentional exposure of human subjects and to persons who submit the results of human research with pesticides to EPA. The amendments broaden the applicability of the rules to cover human testing with pesticides submitted to EPA under any regulatory statute it administers. The amendments also disallow participation in third-party pesticide studies by subjects who cannot consent for themselves. Finally, the amendments identify specific considerations to be addressed in EPA science and ethics reviews of proposed and completed human research with pesticides, drawn from the recommendations of the National Academy of Sciences (NAS). The amendments make no changes to the current Federal Policy for the Protection of Human Subjects (the "Common Rule"), which governs research with human subjects conducted or supported by EPA and many other Federal departments and agencies.

DATES: This rule is effective [*insert date 60 days after date of publication in the* **Federal Register**].

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2010-0785, is available at *http://www.regulations.gov* or at the OPP Docket in the Environmental Protection Agency Docket Center (EPA/DC), located in the EPA West Bldg.,

Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at *http://www.epa.gov/dockets*.

FOR FURTHER INFORMATION CONTACT: Kelly Sherman, Immediate Office of the Director (7501P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 305-8401; fax number: (703) 308-4776; email address: *sherman.kelly@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. Executive Summary

A. Does this Action Apply to Me?

You may be potentially affected by this action if you conduct or sponsor research that may be submitted to EPA and which involves intentional exposure of human subjects. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document might apply to them. Although EPA has in the past received such third-party research from pesticide registrants, other entities could submit such information to EPA.

• Pesticide and other Agricultural Chemical Manufacturing (NAICS code 325320) who sponsor or conduct human research with pesticides.

• Other entities (NAICS code 541710) that sponsor or conduct human research with pesticides, and Institutional Review Boards (IRBs) who review human research with pesticides to ensure it meets applicable standards of ethical conduct. Under these new provisions, EPA must consider the ethical aspects and scientific validity and reliability of research in a manner

that is consistent with the requirements of the Common Rule as codified in 40 CFR part 26, subpart A. The "Common Rule" is the name generally used to refer to the Federal Policy for the Protection of Human Subjects, which governs research with human subjects conducted or supported by EPA and many other Federal departments and agencies. EPA's codification of the Common Rule appears as subpart A in 40 CFR part 26.

B. What Action is the Agency Taking?

The amendments contained in this final rule change the 2006 rule, published in the **Federal Register** issue of February 6, 2006 (71 FR 6138) (FRL-7759-8), subsequently amended in the **Federal Register** issue of June 23, 2006 (71 FR 36171) (FRL-8071-6), and codified at 40 CFR part 26, in the following substantive respects:

• By broadening the applicability of 40 CFR part 26, subparts K, L, M, and Q, so these subparts would apply not only to research submitted to or considered by EPA under the pesticide laws, but also to research involving a "pesticide" (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136(u)) which is submitted to or considered by EPA under any other regulatory statute it administers.

• By incorporating the definition of "pesticide" from FIFRA, as a substance or mixture of substances intended for pesticidal effect.

• By deleting from 40 CFR part 26, subpart K, all references to consent on behalf of a subject in research involving intentional exposure to a pesticide by a subject's "legally authorized representative."

• By incorporating into 40 CFR part 26, subparts P and Q, factors to be considered by EPA and the Human Studies Review Board (HSRB), in their review of proposed and completed human research, derived from the recommendations by the National Research Council of NAS in

its 2004 Report entitled "Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues" (hereafter, 2004 NAS Report) to EPA.

C. What is the Agency's Authority for Taking this Action?

Sections 3(a) and 25(a) of FIFRA (7 U.S.C. 136a(a) and 136w(a)) and section 408(e)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 364a(e)(1)(C)), provide the legal authority for these amendments to the 2006 rule on human research.

D. What are the Incremental Costs and Benefits of this Action?

The incremental costs of these amendments both to industry and to EPA are expected to be negligible. EPA has not, therefore, prepared a new economic analysis for this rule. Because no research has been identified that is outside the scope of the 2006 rule but that would be within the scope of these amendments, EPA has no basis on which to revise the cost estimates that were provided in the economic analysis for the 2006 rule or those most recently provided in the 2008 renewal of the Information Collection Request (ICR) for the existing regulation at 40 CFR part 26. The estimates included in the ICR are summarized in Unit VI.B. and a copy of the ICR is available in the docket.

II. Background

A. EPA's 2006 Rule

As required by section 201 of the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006 (2006 Appropriations Act), Public Law 109-54, 119 Stat. 531, EPA promulgated a rule in 2006 establishing a set of protections for people participating as subjects in third-party human research with pesticides in 40 CFR part 26. (In this context "third-party" research is research neither conducted ("first-party") nor supported ("second-party") by EPA or another Common Rule Federal department or agency.) The 2006 rule prohibits EPA from relying on third-party research on pesticides involving intentional exposure of children or

of pregnant or nursing women, unless relying on the data is crucial to a decision that would impose a more stringent regulatory restriction that would improve protection of public health than could be justified without relying on the data. It further forbids EPA itself to conduct or support any research involving intentional exposure of pregnant or nursing women or of children to any substance.

B. Petition for Review of the 2006 Rule and Settlement Agreement

In early 2006, the Natural Resources Defense Council, Inc.; Pesticide Action Network North American; Pineros y Campesinos Unido Del Noroeste; Physicians for Social Responsibility-San Francisco; Farm Labor Organizing Committee; ALF-CIO; and Migrant Clinicians Network petitioned for review of the 2006 rule in the United States Court of Appeals for the Second Circuit (Second Circuit Court of Appeals) (*NRDC* v. *EPA*, No. 06-0820-ag (2d Cir.)). The Petitioners argued that the 2006 rule violated the 2006 Appropriations Act because it did not bar all pesticide research with pregnant women and children, was inconsistent with the 2004 NAS Report, and was inconsistent with the Nuremburg Code.

After briefing and argument, but before a decision was rendered by the Second Circuit Court of Appeals, EPA and Petitioners entered a settlement agreement in which EPA agreed to conduct notice-and-comment rulemaking on the issue of whether the 2006 rule should be amended. EPA also agreed to propose, at a minimum, amendments to the 2006 rule that were substantially consistent with language negotiated between the parties and attached to the settlement agreement as Exhibit A. This agreement, including Exhibit A, is available in the docket for this action as described under **ADDRESSES**. The settlement agreement makes clear that EPA retained full discretion concerning what amendments were proposed, and what, if any, amendments are finalized.

C. Proposed Amendments to the 2006 EPA Rule

Consistent with the settlement agreement, on January 18, 2011, EPA Administrator Lisa Jackson signed a notice of proposed rulemaking for proposed amendments to the 2006 rule. The proposed amendments were substantially consistent with the regulatory language negotiated with Petitioners. The notice of proposed rulemaking published in the **Federal Register** issue of February 2, 2011 (76 FR 5735) (FRL-8862-7).

D. Retrospective Review of the Common Rule

On July 26, 2011, after issuance of EPA's proposed rule, the Department of Health and Human Services (HHS), in coordination with the Office of Science and Technology Policy (OSTP), issued an advance notice of proposed rulemaking concerning modernization of the Common Rule which governs research with human subjects conducted or supported by EPA and many other Federal departments and agencies (76 FR 44512, July 26, 2011). HHS and OSTP sought comment on "how to better protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators." Id. HHS and OSTP identified seven areas of concern regarding the Common Rule. Most relevant to EPA's proposed amendments to the 2006 rule, was a concern with "the multiple, differing regulatory requirements that can apply to a single research study . . . ." These requirements, according to HHS and OSTP, "have been criticized as complex, inconsistent, and lacking in clarity," and can result in "unwarranted variability across institutions and their [Institutional Review Boards] in how the requirements are interpreted and implemented" (76 FR at 45514). HHS and OSTP stressed the importance of clarifying and harmonizing human subject protections across the Federal Government and sought comment on the means by which this could be accomplished (76 FR at 44528).

III. The Final Rule

EPA is finalizing the amendments to the 2006 rule as proposed. This includes changes to the scope and consent provisions, and the incorporation of selected individual recommendations from the 2004 NAS Report as the specific ethical and scientific factors to be considered by EPA and the HSRB in reviewing proposed and completed human research (i.e., proposed §§ 26.1603 and 26.1703, see 76 FR 5745-5749).

The amendments finalized in this rule are consistent with the recommendations in the 2004 NAS Report and EPA practice under the 2006 rule. That practice has been modeled primarily on EPA's practice under its Common Rule. Sections 26.109, 26.111, 26.116, and 26.117 of EPA's Common Rule explicitly address most of the specific ethical considerations included in the amendments to the 2006 rule, including whether risks to subjects are minimized (compare § 26.1603(c)(2) with existing § 26.111(a)(2)); whether risks are reasonable in comparison to benefits (compare § 26.1603(c)(3) with § 26.111(a)(2)); whether subject selection would be equitable (compare § 26.1603(c)(4) with existing § 26.111(a)(3)); whether consent will be free and voluntary (compare § 26.1603(c)(5) with existing §§ 26.116 and 26.117); whether an appropriately constituted institutional review board (IRB) has reviewed the proposed research (compare § 26.1603(c)(6) with § 26.109); and whether the "special problems" of research involving vulnerable populations are taken into account (compare § 26.1603(c)(7) and (8) with existing § 26.111(a)(3)). Other considerations are implicitly addressed.

The Common Rule's requirement to "minimize risks" in § 26.111(a)(1) necessitates consideration of whether adequate animal data is available to assess potential risks to subjects (see § 26.1603(c)(1)). It would involve consideration of whether medical care is to be provided for injuries incurred in the proposed research (see § 26.1603(c)(10)). Section 26.111(b)'s requirement that additional safeguards be in place to protect against undue influence of

"economically" disadvantaged persons ensures that consideration of whether any proposed payments are so high as to constitute undue inducement or so low as to be attractive only to individuals who are socioeconomically disadvantaged (see § 26.1603(c)(9)). Although scientific considerations are not addressed in similar detail in the Common Rule requirements, nonetheless, the requirement to consider scientific validity and reliability and the Common Rule's emphasis on the need for "sound research design" in § 26.111(a)(1) and the need to take "the importance of the knowledge that may reasonably be expected to result" from the study into account, mandate that EPA focus on considerations addressing scientific validity such as those included in §§ 26.1603 and 26.1703. At a minimum, NAS Recommendations 3-1, 4-1, 5-1, 5-2, 5-3, and 5-5 are critical to proper consideration of the Common Rule's ethical requirements and its requirement for "sound research design."

IV. Public Comments on the Proposed Amendments

This unit discusses, in general terms, the public comments on the proposed amendments and EPA's responses to those comments. EPA received a total of 10 public comments on the proposed amendments during the 60-day comment period. Comments were submitted by 4 individual citizens and 6 different entities – the Agricultural Handler Exposure Task Force, the American Chemistry Council (on behalf of the Antimicrobial Exposure Assessment Task Force II), Beyond Pesticides, CropLife America, Natural Resources Defense Council, and SC Johnson & Son, Inc. The docket (under docket ID number EPA-HQ-OPP-2010-0785) includes all of the comments submitted to EPA on the proposed amendments, as well as EPA's Response to Comments document, which provides detailed responses to all comments received.

A. Comments on Proposal to Expand Scope to Include Research Submitted to EPA under Any Regulatory Statute EPA Administers

Two comments addressed the proposed changes to the scope of the 2006 rule. One

commenter stated that the 2006 Appropriations Act did not permit an expansion of scope beyond pesticide studies performed in the FIFRA and FFDCA context, and another argued that the 2006 Appropriations Act required that the scope of the rule be further expanded beyond studies submitted, or intended for submission, to EPA.

After considering these comments, EPA has decided to finalize the rule text relating to scope as it was proposed, i.e., expanding the scope to cover research involving intentional exposure of human subjects to pesticides where that research is submitted, or intended to be submitted, to EPA under any regulatory statute that EPA administers. As noted in EPA's Response to Comments document, EPA no longer regards the 2006 Appropriations Act as authority for this rule. Therefore, EPA believes it is unnecessary to address whether the 2006 Appropriation Act either requires or does not allow EPA to establish a different scope for this rule.

Nevertheless, EPA regards FIFRA as providing adequate legal authority for the scope of research covered by this final rule. Sections 3(a) and 25(a) of FIFRA provide EPA with authority to regulate pesticides, including research involving intentional exposure of a human subject to a substance, when the substance is being tested as a "pesticide." That includes research intended for submission to EPA, whether under FIFRA, FFDCA, or any of EPA's other regulatory authorities. EPA believes it makes sense to apply the same standards to all human studies involving pesticides submitted to EPA. On the other hand, EPA believes that it is not in the public interest to extend the prohibition against research involving intentional exposure of children or pregnant women to pesticides beyond the scope delineated in the proposed rule because such a prohibition, if enforceable, could have the unintended effect of prohibiting valuable research.

B. Comments on Inclusion of NAS-Derived Considerations

Two commenters questioned whether new regulatory text proposed at § 26.1603(b)(2)(ii) and (iii) would change the ways in which EPA has been reviewing proposed studies to measure exposures experienced by people who mix, load, or apply pesticides. As proposed, EPA would have been required to consider whether the proposed research includes representative study populations for the endpoint in question and has adequate statistical power to detect appropriate effects. These commenters expressed the same concern regarding the proposed regulatory text at § 26.1703(a)(2) and (3), which would require EPA to consider these factors in determining whether to rely on the research. As explained in more detail in EPA's Response to Comments document, EPA does not believe that the adoption of the specific ethical and scientific factors will impose any additional burden on sponsors of exposure studies or on the types of exposure studies referenced by the commenters.

As explained previously, EPA has decided to finalize the proposed text detailing specific scientific and ethical aspects of proposed and completed research – including the text proposed at § 26.1603(b)(2)(ii) and (iii) and at § 26.1703(a)(2) and (3) – that EPA and the HSRB must consider when reviewing such research. EPA also notes that, under the 2006 rule as amended through this final rule, EPA does not intend to change the way in which it reviews exposure research with respect to the inclusion of representative populations or the statistical power of the study, although EPA will consider whether further guidance on this issue is needed. In addition, EPA does not believe the codification of the specific ethical and scientific factors derived from the 2004 NAS Report represents a material change in the way a particular pesticide study would have been reviewed. Thus, EPA believes that particular pesticides studies that have been approved under the 2006 rule, would also meet the standards reflected in this final rule.

C. Other Comments, Including Comments on Narrowing the Scope of the 2006 Rule to Include Only Intentional Dosing Studies

The remainder of the public comments addressed issues beyond the scope of the proposed amendments. These comments included arguments that the burden of the requirements of the 2006 rule (as opposed to any burden connected to this amendment) are unjustified, and assertions that EPA's interpretation in the 2006 rule of the language "research involving intentional exposure of a human subject" incorrectly expanded the scope of the rule beyond that required in the 2006 Appropriations Act, which addressed only "intentional dosing human toxicity studies." The commenters are referring to § 26.1101(a) of the 2006 rule, which defines the scope of the rule as applying to "all research initiated after April 7, 2006 involving intentional exposure of a human subject …." As EPA explained in the preamble to the proposal for the 2006 rule, this scope was intended to capture "all intentional dosing human studies intended for submission to EPA under the pesticide laws", i.e., studies involving intentional dosing to measure a toxic effect and studies involving intentional dosing to measure other scientific endpoints, like exposure (**Federal Register** issue of September 12, 2005 (70 FR at 53845) (FRL-7728-2)). Additional discussion in the preambles to the proposal for the 2006 rule and 2006 rule further explains what studies EPA intended to be included within the scope of the 2006 rule (70 FR at 53845-53847; 71 FR 6138, 6146, 6149-6150).

Because these comments were directed at provisions in the 2006 rule that EPA did not reopen for reconsideration as part of the proposed amendments, these comments are beyond the scope of this final rule, and no response to them is required to finalize this rule. Nonetheless, EPA appreciates the concerns expressed by the commenters with regard to the burdens imposed by the 2006 rule and recognizes that there may be value in considering further amendments to

the 2006 rule in a way that reduces the burdens on investigators, e.g., by limiting the types of research that are subject to particular requirements of the rule.

V. Conclusion

EPA received relatively few comments on the proposed rule, and many of the comments received did not address the amendments in the proposal. For the reasons noted previously, the comments that did address the proposal do not merit any change to the amendments as proposed. Accordingly, EPA is finalizing the amendments as proposed for the reasons stated herein and in the preamble to the proposed rule.

VI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

Under Executive Order 12866 (58 FR 51735, October 4, 1993), this action is a "significant regulatory action," because the Office of Management and Budget (OMB) determined that it would raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order. Accordingly, EPA submitted this action to OMB for review under Executive Orders 12866 and 13563 (76 FR 3821, January 21, 2011). Any changes made in response to OMB recommendations have been documented in the docket for this rulemaking as required by the Executive Order.

B. Paperwork Reduction Act (PRA)

This action does not impose any new information collection burden that would require additional review or approval by OMB. However, OMB has previously approved the information collection requirements contained in the existing regulations at 40 CFR part 26 under the provisions of PRA (44 U.S.C. 3501 *et seq*.), and has assigned OMB Control No. 2070-0169 (EPA ICR No. 2195). The OMB control numbers for EPA's regulations in 40 CFR are

listed in 40 CFR part 9.

In its 2008 analysis supporting the most recent renewal of this ICR, EPA estimated that respondents would submit to the Agency some 34 proposals for or reports of research involving intentional exposure of human subjects each year. EPA estimated that preparation of information required by the 2006 rule would require about 598 hours per study at a cost of $45,927 per study, for a total estimated annual burden for affected entities of 20,332 hours at an estimated cost of $1,561,518. In addition, EPA estimated annual submission of 20 reports of research requiring only documentation of ethical conduct at a cost of 12 hours/$879 per report, or 240 hours/$17,580 per year. The total estimate of the annual respondent burden and cost was the sum of these two estimates, or 2,572 hours/$1,579,098.

These paperwork burden and cost estimates include activities related to initial rule familiarization, as well as activities that researchers would have to perform even without the Agency's rulemaking in this area, such as developing a protocol and maintaining records.

The average annual burden on EPA for reviewing each of the 34 study submissions was estimated to be 178 hours/$16,850 per study, or 6,052 hours/$572,900 per year. The average annual burden on EPA for reviewing each of the 20 additional submissions was estimated to be 44 hours/$3,158 per study, or 880 hours/$63,160 per year. The total estimate of the annual burden on EPA was the sum of these two estimates, or 6,932 hours/$636,000 per year.

In no year since promulgation of the 2006 rule have more than 7 protocols been submitted to EPA by industry; the average annual rate has been just over 5 for the 5-year period of 2006-2010. Somewhat fewer completed reports have been submitted during this period, so the average of new protocols and finished studies has been about 11 per year, less than a third of the projected 34 per year covered by the ICR. There is no evidence to suggest an upward trend, and nothing in these amendments is believed likely to lead to a significant change in the rate of

protocol and study submissions.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for EPA's regulations in 40 CFR are listed in 40 CFR part 9.

C. Regulatory Flexibility Act (RFA)

RFA (5 U.S.C. 601 *et seq*.), generally requires an agency to prepare a regulatory flexibility analysis of any rule subject to notice and comment rulemaking requirements under the Administrative Procedure Act (5 U.S.C. 551-553) or any other statute unless the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Small entities include small businesses, small organizations, and small governmental jurisdictions.

For purposes of assessing the impacts of this rule on small entities, small entity is defined as:

1. A small business as defined by the Small Business Administration's (SBA) regulations at 13 CFR 121.201, which is based on either the maximum number of employees or on the sales for small businesses in each industry sector, as defined by a 6-digit NAICS code, and for this rule is pesticide and other agricultural chemical manufacturers (NAICS code 325320) who sponsor or conduct human research with pesticides, or other entities (NAICS code 541710) that sponsor or conduct human research with pesticides, and IRBs who review human research with pesticides to ensure it meets applicable standards of ethical conduct;

2. A small governmental jurisdiction that is a government of a city, county, town, school district, or special district with a population of less than 50,000; or

3. A small organization that is any not-for-profit enterprise which is independently owned and operated and is not dominant in its field.

After considering the economic impacts of this final rule on small entities, I certify that this action will not have a significant economic impact on a substantial number of small entities. Because no small entities have been identified that are directly regulated by these amendments, EPA has not attempted to reduce the impact of this final rule on small entities. Public comments were explicitly invited on all aspects of the proposal and its impacts on small entities, but no such comments were received.

D. Unfunded Mandates Reform Act (UMRA)

Title II of UMRA (2 U.S.C. 1531-1538) establishes requirements for Federal agencies to assess the effects of their regulatory actions on State, local, and tribal governments and the private sector. This rule does not contain a Federal mandate that may result in expenditures of $100 million or more for State, local, and tribal governments, in the aggregate, or the private sector in any 1 year. Thus, this rule is not subject to the requirements of UMRA sections 202 or 205. This rule is also not subject to the requirements of UMRA section 203, because it contains no regulatory requirements that might significantly or uniquely affect small governments. These amendments are unlikely to affect State, local, and tribal governments at all, and are likely to affect the private sector only trivially.

E. Executive Order 13132: Federalism

This action does not have federalism implications because it will not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132 (64 FR 43255, August 10, 1999). It makes marginal changes in the scope of an existing rule applying to sponsors and investigators conducting certain kinds of research involving human subjects, and refines the standards for EPA oversight of and reliance on such research. Thus, Executive Order 13132 does not apply to this action.

F. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

This action does not have tribal implications as specified in Executive Order 13175 (65 FR 67249, November 9, 2000). This action will not have substantial direct effects on Indian Tribes, will not significantly or uniquely affect the communities of Indian tribal governments, and does not involve or impose any requirements that affect Indian Tribes. Thus, Executive Order 13175 does not apply to this action.

G. Executive Order 13045: Protection of Children from Environmental Health Risks and Safety Risks

EPA interprets Executive Order 13045 (62 FR 19885, April 23, 1997), as applying only to those regulatory actions that concern health or safety risks, such that the analysis required under section 5-501 of the Executive Order has the potential to influence the regulation. This action is not subject to Executive Order 13045, because it does not establish an environmental standard intended to mitigate health or safety risks, nor is it an "economically significant regulatory action" as defined in Executive Order 12866. The 2006 rule applies to the conduct and review of research involving intentional exposure of human subjects, and prohibits the conduct of or EPA reliance on any such research involving subjects who are children, or pregnant or nursing women. These provisions would not be affected by the amendments.

H. Executive Order 13211: Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use

This action is not a "significant regulatory action" as defined in Executive Order 13211 (66 FR 28355, May 22, 2001), because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

I. National Technology Transfer and Advancement Act (NTTAA)

Section 12(d) of NTTAA (15 U.S.C. 272 note) directs EPA to use voluntary consensus standards in its regulatory activities unless to do so would be inconsistent with applicable law or

otherwise impractical. Voluntary consensus standards are technical standards (e.g., materials specifications, test methods, sampling procedures, and business practices) that are developed or adopted by voluntary consensus standards bodies. NTTAA directs EPA to provide Congress, through OMB, explanations when the Agency decides not to use available and applicable voluntary consensus standards. This action does not involve any technical standards. Therefore, EPA did not consider the use of any voluntary consensus standards.

J. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

Executive Order 12898 (59 FR 7629, February 16, 1994) establishes Federal executive policy on environmental justice. Its main provision directs Federal agencies, to the greatest extent practicable and permitted by law, to make environmental justice part of their mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of their programs, policies, and activities on minority populations and low-income populations in the United States.

EPA has determined that this final rule will not have disproportionately high and adverse human health or environmental effects on minority or low-income populations, because it does not affect the level of protection provided to human health or the environment. This rule does not entail special considerations of environmental justice related issues. The strengthened protections for human subjects participating in covered research established in the 2006 rule will not be altered by these amendments.

VII. Congressional Review Act

The Congressional Review Act (5 U.S.C. 801 *et seq*.), generally provides that before a rule may take effect, the agency promulgating the rule must submit a rule report, which includes a copy of the rule, to each House of the Congress and the Comptroller General of the United

States. EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the **Federal Register**. A major rule cannot take effect until 60 days after it is published in the **Federal Register**. This action is not a "major rule" as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 26

Environmental protection, Administrative practice and procedures, Human research, Pesticides and pests.

Dated: February 8, 2013.

Lisa P. Jackson,

Administrator.

Therefore, 40 CFR chapter I is amended as follows:

PART 26--[AMENDED]

1. The authority citation for part 26 is revised to read as follows:

Authority: 5 U.S.C. 301; 7 U.S.C. 136a(a) and 136w(a)(1); 21 U.S.C. 346a(e)(1)(C); sec. 201, Pub. L. 109-54, 119 Stat. 531; and 42 U.S.C. 300v-1(b).

2. In § 26.1101:

a. Remove paragraphs (a), (c), and (g).

b. Redesignate paragraph (b) as (c), (f) as (g), (e) as (f), and (d) as (e).

c. Add new paragraphs (a), (b), and (d).

The amendments read as follows:

§ 26.1101 To what does this subpart apply?

(a) Except as provided in paragraph (c) of this section, this subpart applies to all research initiated on or after [*insert date 60 days after date of publication in the* **Federal Register**] involving intentional exposure of a human subject to:

(1) Any substance if, at any time prior to initiating such research, any person who conducted or supported such research intended either to submit results of the research to EPA for consideration in connection with any action that may be performed by EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136-136y) or section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 346a), or to hold the results of the research for later inspection by EPA under FIFRA or section 408 of FFDCA; or

(2) A pesticide if, at any time prior to initiating such research, any person who conducted or supported such research intended either to submit results of the research to EPA for consideration in connection with any action that may be performed by EPA under any regulatory statute administered by EPA other than those statutes designated in paragraph (a)(1) of this

section, or to hold the results of the research for later inspection by EPA under any regulatory statute administered by EPA other than those statutes designated in paragraph (a)(1) of this section.

(b) For purposes of determining a person's intent under paragraph (a) of this section, EPA may consider any available and relevant information. EPA must rebuttably presume the existence of intent if:

(1) The person or the person's agent has submitted or made available for inspection the results of such research to EPA; or

(2) The person is a member of a class of people who, or whose products or activities, are regulated by EPA and, at the time the research was initiated, the results of such research would be relevant to EPA's exercise of its regulatory authority with respect to that class of people, products, or activities.

* * * * *

(d) The EPA Administrator retains final judgment as to whether a particular activity is covered by this subpart.

* * * * *

3. In § 26.1102, revise paragraphs (a) and (c) and add new paragraph (k) to read as follows:

§ 26.1102 Definitions.

(a) *Administrator* means the Administrator of the Environmental Protection Agency (EPA) and any other officer or employee of EPA to whom authority has been delegated.

* * * * *

(c) *Pesticide* means any substance or mixture of substances meeting the definition in 7 U.S.C. 136(u) (Federal Insecticide, Fungicide, and Rodenticide Act, section 2(u)).

* * * * *

(k) *Common Rule* refers to the Federal Policy for the Protection of Human Subjects that was established in 1991 by the Office of Science and Technology Policy and codified in 1991 by EPA and 14 other Federal departments and agencies (see the **Federal Register** issue of June 18, 1991 (56 FR 28003)) and subsequently codified by other Federal departments and agencies. The Common Rule contains a widely accepted set of standards for conducting ethical research with human subjects, together with a set of procedures designed to ensure that the standards are met. Once codified by a Federal department or agency, the requirements of the Common Rule apply to research conducted or sponsored by that Federal department or agency. EPA's codification of the Common Rule appears in 40 CFR part 26, subpart A.

§ 26.1111 [Amended]

4. In § 26.1111, remove from paragraph (a)(4) the phrase "or the subject's legally authorized representative."

5. In § 26.1116, revise the introductory text of the section to read as follows:

§ 26.1116 General requirements for informed consent.

No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject. An investigator must seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject must be in language understandable to the subject. No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

* * * * *

6. Revise § 26.1117 to read as follows:

§ 26.1117 Documentation of informed consent.

(a) Informed consent must be documented by the use of a written consent form approved by the IRB and signed by the subject. A copy shall be given to the subject.

(b) The consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 26.1116. This form may be read to the subject, but in any event, the investigator must give the subject adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by § 26.1116 have been presented orally to the subject. When this method is used, there must be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject. Only the short form itself is to be signed by the subject. However, the witness must sign both the short form and a copy of the summary, and the person actually obtaining consent must sign a copy of the summary. A copy of the summary must be given to the subject, in addition to a copy of the short form.

7. Revise the heading for subpart L to read as follows:

Subpart L--Prohibition of Third-Party Research Involving Intentional Exposure to a Pesticide of Human Subjects Who are Children or Pregnant or Nursing Women

8. Revise § 26.1201 to read as follows:

§ 26.1201 To what does this subpart apply?

This subpart applies to any research subject to subpart K of this part.

9. Revise § 26.1301 to read as follows:

§ 26.1301 To what does this subpart apply?

This subpart applies to any person who submits to EPA on or after [*insert date 60 days*

after date of publication in the **Federal Register**] either of the following:

(a) A report containing the results of any human research for consideration in connection with an action that may be performed by EPA under FIFRA (7 U.S.C. 136-136y) or section 408 of FFDCA (21 U.S.C. 346a).

(b) A report containing the results of any human research on or with a pesticide for consideration in connection with any action that may be performed by EPA under any regulatory statute administered by EPA.

§ 26.1302 [Amended]

10. In § 26.1302, remove the word "shall."

§ 26.1502 [Amended]

11. In § 26.1502:

a. Remove in the first sentence of paragraph (a), the period after the phrase "during an inspection" and add in its place a comma**.**

b. Remove in the second sentence of paragraph (a), the phrase "The agency" and add in its place "EPA."

c. Remove in the last sentence of the introductory text of paragraph (b), the phrase "the Agency" and add in its place "EPA."

§ 26.1505 [Amended]

12. In § 26.1505, remove from the last sentence, the citation "§ 26.1502(c)" and add in its place "§ 26.1502(b)(4)."

§ 26.1507 [Amended]

13. In § 26.1507, remove from the last sentence, the phrase "The Agency" and add in its place "EPA."

§§ 26.1601 through 26.1603 [Redesignated as §§ 26.1603 through 26.1605]

14. Redesignate §§ 26.1601 through 26.1603 as §§ 26.1603 through 26.1605.

15. Add new §§ 26.1601 and 26.1602 to subpart P to read as follows:

§26.1601 To what does this subpart apply?

This subpart applies to both of the following:

(a) Reviews by EPA and by the Human Studies Review Board of proposals to conduct new research subject to § 26.1125.

(b) Reviews by EPA on or after [*insert date 60 days after date of publication in the* **Federal Register**] and, to the extent required by § 26.1604, by the Human Studies Review Board of reports of completed research subject to § 26.1701.

§ 26.1602 Definitions.

The definitions in § 26.1102 also apply to this subpart.

16. In newly redesignated § 26.1603:

a. Remove paragraphs (a) and (e).

b. Redesignate paragraphs (b) through (d) as (e) through (g).

c. Add new paragraphs (a), (b), (c), (d), and (h).

The amendments read as follows:

§ 26.1603 EPA review of proposed human research.

(a) EPA must review all proposals for new human research submitted under § 26.1125 in a timely manner.

(b) In reviewing proposals for new human research submitted under § 26.1125, the EPA Administrator must consider and make determinations regarding the scientific validity and reliability of the proposed research, including:

(1) Whether the research would be likely to produce data that address an important scientific or policy question that cannot be resolved on the basis of animal data or human

observational research.

(2) Whether the proposed research is designed in accordance with current scientific standards and practices to:

(i) Address the research question.

(ii) Include representative study populations for the endpoint in question.

(iii) Have adequate statistical power to detect appropriate effects.

(3) Whether the investigator proposes to conduct the research in accordance with recognized good research practices, including, when appropriate, good clinical practice guidelines and monitoring for the safety of subjects.

(c) In reviewing proposals for new research submitted under § 26.1125, the EPA Administrator must consider and make determinations regarding ethical aspects of the proposed research, including:

(1) Whether adequate information is available from prior animal studies or from other sources to assess the potential risks to subjects in the proposed research.

(2) Whether the research proposal adequately identifies anticipated risks to human subjects and their likelihood of occurrence, minimizes identified risks to human subjects, and identifies likely benefits of the research and their distribution.

(3) Whether the proposed research presents an acceptable balance of risks and benefits. In making this determination for research intended to reduce the interspecies uncertainty factor in a pesticide risk assessment, the EPA Administrator will also consider the process laid out and the attendant discussion for evaluating that type of study as provided in Recommendation 4-1 of the 2004 Report from the National Research Council of the National Academy of Sciences (NAS), entitled “Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues.”

(4) Whether subject selection will be equitable.

(5) Whether subjects' participation would follow free and fully informed consent.

(6) Whether an appropriately constituted IRB or its foreign equivalent has approved the proposed research.

(7) If any person from a vulnerable population may become a subject in the proposed research, whether there is a convincing justification for selection of such a person, and whether measures taken to protect such human subjects are adequate.

(8) If any person with a condition that would put them at increased risk for adverse effects may become a subject in the proposed research, whether there is a convincing justification for selection of such a person, and whether measures taken to protect such human subjects are adequate.

(9) Whether any proposed payments to subjects are consistent with the principles of justice and respect for persons, and whether they are so high as to constitute undue inducement or so low as to be attractive only to individuals who are socioeconomically disadvantaged.

(10) Whether the sponsor or investigator would provide needed medical care for injuries incurred in the proposed research, without cost to the human subjects.

(d) With respect to any research or any class of research subject to this subpart, the EPA Administrator may recommend additional conditions which, in the judgment of the EPA Administrator, are necessary for the protection of human subjects.

* * * * *

(h) EPA must provide the submitter of the proposal copies of the EPA and Human Studies Review Board reviews.

17. In newly redesignated § 26.1604, revise paragraph (a) to read as follows:

§ 26.1604 EPA review of completed human research.

(a) When considering, under any regulatory statute it administers, data from completed research involving intentional exposure of humans to a pesticide, EPA must thoroughly review the material submitted under § 26.1303, if any, and other available, relevant information and document its conclusions regarding the scientific and ethical conduct of the research.

* * * * *

18. Add §§ 26.1606 and 26.1607 to subpart P to read as follows:

§ 26.1606 Human Studies Review Board review of proposed human research.

In commenting on proposals for new research submitted to it by EPA, the Human Studies Review Board must consider the scientific merits and ethical aspects of the proposed research, including all elements required in § 26.1603(b) and (c) and any additional conditions recommended pursuant to § 26.1603(d).

§ 26.1607 Human Studies Review Board review of completed human research.

In commenting on reports of completed research submitted to it by EPA, the Human Studies Review Board must consider the scientific merits and ethical aspects of the completed research, and must apply the appropriate standards in subpart Q of this part.

19. Revise the heading for subpart Q to read as follows:

Subpart Q--Standards for Assessing Whether to Rely on the Results of Human Research in EPA Actions

20. Revise §§ 26.1701 through 26.1705 to read as follows:

* * * * *

Sec.

adults initiated after April 7, 2006.

* * * * *

§ 26.1701 To what does this subpart apply?

(a) For decisions under FIFRA (7 U.S.C. 136-136y) or section 408 of FFDCA (21 U.S.C. 346a), this subpart applies to research involving intentional exposure of human subjects to any substance.

(b) For decisions under any regulatory statute administered by EPA other than those statutes designated in paragraph (a) of this section, this subpart applies to research involving intentional exposure of human subjects to a pesticide.

§ 26.1702 Definitions.

The definitions in § 26.1102 and § 26.1202 also apply to this subpart.

§ 26.1703 Prohibitions applying to all research subject to this subpart.

(a) Prohibition of reliance on scientifically invalid research. EPA must not rely on data from research subject to this subpart unless EPA determines that the data are relevant to a scientific or policy question important for EPA decisionmaking, that the data were derived in a manner that makes them scientifically valid and reliable, and that it is appropriate to use the data for the purpose proposed by EPA. In making such determinations, EPA must consider:

(1) Whether the research was designed and conducted in accordance with appropriate scientific standards and practices prevailing at the time the research was conducted.

(2) The extent to which the research subjects are representative of the populations for the endpoint or endpoints in question.

(3) The statistical power of the data to support the scientific conclusion EPA intends to draw from the data.

(4) In a study that reports only a No Observed Effect Level (NOEL) or a No Observed

Adverse Effect Level (NOAEL), whether a dose level in the study gave rise to a biological effect, thereby demonstrating that the study had adequate sensitivity to detect an effect of interest.

(b) Prohibition of reliance on research subject to this subpart involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children. Except as provided in § 26.1706, EPA must not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

§ 26.1704 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults.

(a) This section applies to research subject to this subpart that is not subject to § 26.1705.

(b) Except as provided in § 26.1706, EPA must not rely on data from any research subject to this section if there is clear and convincing evidence that:

(1) The conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent); or

(2) The conduct of the research was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.

(c) The prohibition in this section is in addition to the prohibitions in § 26.1703.

§ 26.1705 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults initiated after April 7, 2006.

(a) This section applies to research subject to this subpart, that:

(1) Was initiated after April 7, 2006.

(2) Was subject, at the time it was conducted, either to subparts A through L of this part,

or to the codification of the Common Rule by another Federal department or agency.

(b) Except as provided in § 26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with either:

(1) All applicable provisions of subparts A through L of this part, or the codification of the Common Rule by another Federal department or agency; or

(2) If the research was conducted outside the United States, with procedures at least as protective of subjects as those in subparts A through L of this part, or the codification of the Common Rule by another Federal department or agency.

(c) Except as provided in § 26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with either:

(1) A proposal that was found to be acceptable under § 26.1603(c), and no amendments to or deviations from that proposal placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent. If EPA discovers that the submitter of the proposal materially misrepresented or knowingly omitted information that would have altered the outcome of EPA's evaluation of the proposal under § 26.1603(c), EPA must not rely on that data.

(2) A proposal that would have been found to be acceptable under § 26.1603(c), if it had been subject to review under that section, and no amendments to or deviations from that proposal placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.

(d) The prohibition in this section is in addition to the prohibitions in § 26.1703.

§ 26.1706 [Amended]

21. In § 26.1706, remove in paragraph (d) the word “publishes” and add in its place the phrase “has published.”

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