EXAMPLES OF EPA USE OF CLINICAL HUMAN TEST DATA

There follow some detailed citations and quotations for examples of instances in which human volunteer test data played a significant or substantial role in setting of a regulatory standard by EPA. Some such examples include controlled human volunteer studies involving exposures to MTBE and particulates supported or conducted by EPA's Human Studies Division of its National Health and Environmental Effects Research Laboratory ("NHEERL").[1]

These examples are only from EPA programs. Other examples of support for human volunteer testing and use of such test data in standards-setting could be provided from other Federal agencies.

For several of the substances below, human volunteer test data which had previously been a principal factor in determining a consensus LOAEL and/or NOAEL and RfD (reference dose) for regulatory purposes, as recorded in the Agency's public IRIS database, was later explicitly excluded from a regulatory decision based on uncertainty over the position the Agency would take on acceptability of such data following its July 27, 1998 expression of concern over the use of such data. That situation, of course, remains unresolved.

Also, in the case of several of the pesticides, only the current RfD or a drinking water standard is available for purposes of preparing this document. While tolerances for residues have previously been set for such pesticides, the *Federal Register* tolerance notices do not provide any information on the scientific basis, and many of the underlying risk assessments are not available on the Internet and would have to be obtained through a freedom of information request. In the interests of expediency, therefore, we have not waited to obtain FOIA information for those pesticides and have assumed that, consistent with its usual approach prior to July 27, 1998, the Agency employed the consensus RfD in setting the crop tolerances. We believe this assumption is appropriate given that much of the debate over the use of human volunteer studies of pesticides has been in the context of determining LOAELs, LOELs, NOAELs, and NOELs, as well as simply the ethics of enrolling volunteers to allow themselves to be exposed to potentially toxic chemicals.

This document is not comprehensive in that it does not investigate regulatory standards for some other programs such as CERCLA and RCRA. Instead, it relies on recognition that EPA's IRIS RfDs are a primary determinant in setting all of the Agency's regulatory standards

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[1] See, e.g., Prah JD, Goldstein GM, Devlin R, Ashley D, House D, Cohen KL, and Gerrity T. 1994. Sensory, symptomatic, inflammatory, and ocular responses to and the metabolism of methyl tertiary butyl ether in a controlled human exposure experiment. *Inhal Toxicol* 6:521-38; "Oxygenates in Water: Critical Information and Research Needs", EPA/600/R-98/048, Dec. 1998, p. 25.

for non-cancer health risks.

The substance-specific information below on use of human volunteer test data in setting regulatory standards or RfDs is presented alphabetically.

1. Aldicarb, aldicarb sulfoxide, and aldicarb sulfone

Aldicarb is a carbamate insecticide. On July 1, 1991 (56 Fed.Reg. 30266), EPA set MCLGs and MCLs[2] for aldicarb and its metabolites. The MCLGs were based on the RfD as adjusted with standard uncertainty factors and exposure adjustments. The RfD of 0.0002 mg/kg/day and MCLG of 0.001 mg/l for aldicarb and aldicarb sulfoxide were derived from no-effect levels observed in an experimental animal study and a human volunteer study involving four healthy male volunteers (Haines, 1971). At 30269. Although aldicarb sulfone was considered to be less toxic, the same MCLG was set for it using a higher uncertainty factor because the MCLG was based solely on the NOAEL in an animal study and there were no human clinical data available as there were for aldicarb and aldicarb sulfoxide. The Agency indicated in the earlier rulemaking proposal that "[i]f human data with aldicarb sulfone become available to the Agency, the extra 3-fold [sic] used in the RfD calculation for aldicarb sulfone may not be necessary." 56 Fed.Reg. 3600, 3606 (Jan. 30, 1991).

In 1992, as reflected in EPA's online IRIS database, a new human volunteer study for acute human oral exposure to aldicarb was submitted to EPA. The study was a double-blind, placebo-controlled study involving 38 men and 6 women. (Cited in the IRIS entry as Rhone-Poulenc Ag Company. 1992. A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers. Inveresk Clinical Research Report No. 7786, MRID No. 423730-01. HED Doc. No. 0010459.) The IRIS database shows that the RfD for aldicarb was revised on 11/01/1993 to 0.001 using this new human volunteer study as the principal study, vs. the 0.0002 RfD used for the July 1, 1991 final drinking water MCLG, and using an uncertainty factor of 10, rather than the UF of 100 that was used for the MCLG.[3]

2. Barium and barium compounds

Barium and barium compounds are a metal and its soluble salts that are found in groundwater in many parts of the country due to various industrial processes. On July 1, 1991, EPA set a final drinking water MCLG for barium and barium compounds based on an RfD of

[2] MCLs (maximum contaminant levels) are set "as close as feasible" to the MCLGs (maximum contaminant level goals).

[3] On May 27, 1992, EPA "postponed" the drinking water standards for aldicarb and its metabolites, but kept monitoring requirements in place. 57 Fed.Reg. 110551 et seq. No further action has been taken by EPA on these drinking water standards.

0.07 mg/kg/day derived from a human volunteer study in which barium chloride in drinking water was administered to 11 healthy male volunteers (cited in the IRIS database as "Wones, RG,; Stadler, BL; Frohman, LA. (1990) Lack of effect of drinking water barium on cardiovascular risk factor. Environ Health Perspect 85:355-59", and cited in the EPA final drinking water rule as "Wones 1990".) An uncertainty factor of 3 was applied to the NOAEL. 56 Fed.Reg. 30266, 30272.

The latest IRIS database entry for barium and barium compounds, last revised 1/21/99, continues to show an RfD of 0.07 using an uncertainty factor of 3. Unlike the 1991 drinking water final rule (above), however, it does not state that the RfD is based solely on the Wones et al. 1990 human volunteer study; rather, it states: "No single study is appropriate as the basis for a lifetime RfD for barium. The RfD is based on a weight-of-evidence approach that focuses on four co-principal studies: the Wones et al. (1990) experimental study in humans, the Brenniman and Levy (1984) epidemiologic study, and the subchronic and chronic rat studies that employed adequate diets and investigated both cardiovascular and renal endpoints (NTP, 1994)."

3. Baygon (propoxur)

Baygon is a carbamate insecticide. However, because it is not used on crops, no tolerance for residues have been set. EPA's online IRIS database shows that the RfD, last revised 07/01/1992, was based on a single human volunteer study in which an unspecified number of subjects received a single oral dose. A NOEL could not be determined, and the RfD was based on an LEL with an uncertainty factor of 100. The study is cited as "Vandekar, M., R. Plestina and K. Wilhelm. 1971. Toxicity of carbamates for mammals. Bull. World. Health. Org. 44:241-249."

4. Carbon monoxide

EPA set air quality standards (NAAQS) for carbon monoxide in 1971. In 1985, it completed a review of the standards and decided not to revise the 1971 standard and to revoke the secondary standard. In 1994, EPA completed another review of the NAAQS and determined that revisions were not appropriate. 59 Fed. Reg. 38906 et seq. (Aug. 1, 1994). The 1994 decision was based primarily on controlled human volunteer studies of patients suffering from angina pectoris, ischemic heart disease, and obstructive coronary artery disease. 59 Fed.Reg. at 38909-11. The data from those studies were supported by numerous controlled human volunteer studies of the effects of carbon monoxide on oxygen uptake and exercise performance in healthy individuals. 59 Fed.Reg. at 38909, 38911. The notice of the final decision also discussed the findings from numerous controlled human volunteer studies for neurobehavioral effects such as changes in visual perception, hearing, motor performance, sensorimotor performance, and vigilance, but concluded that because the cardiovascular studies showed effects at lower levels, they should remain the primary focus. 59 Fed.Reg. at 38911.

Air quality standards, and reviews of those standards, are based on "Criteria Documents", followed by "Staff Papers", and supplemented by CASAC evaluation of the those two documents. The most recent Criteria Document for carbon monoxide was published in June 2000. AIR QUALITY CRITERIA FOR CARBON MONOXIDE. USEPA EPA 600/P-99/001F. 01, June 2000. That CD states that the "[h]ealth assessment provided in this document supports and substantiates the conclusions drawn in the previous [criteria] document." (Abstract.) The previous criteria document was completed in 1991 and was one of the source documents for the review discussed above that was completed in 1994. The 2000 CD goes on to state: "Although the scientific data have changed little since 1991, controlled-exposure studies continue to provide the most quantitative evidence on low-level CO effects in humans. *Id.*, section 6.1 ("Health Effects of Exposure to Carbon Monoxide"), p. 6-1.

5. Chlorpyrifos

Chlorpyrifos is an organophosphate insecticide. EPA's online IRIS database shows that the oral RfD for chlorpyrifos was last revised in 1988. The RfD was set at 0.003 mg/kg/day, using a NOEL of 0.03 mg/kg/day and a LOEL of 0.10 mg/kg/day, and an uncertainty factor of 10. The NOEL and LOEL are based on a controlled human volunteer study of 16 males treated for 20 days at a low and mid-range doses, and for 9 days at a higher dose. This "principal study" for the RfD is cited as "Dow Chemical Company. 1972. Accession No. 112118." This RfD has presumably been the basis for tolerances assigned to the product.

On June 8, 2000, EPA published (and subsequently made available online) a revised Human Health Risk Assessment for chlorpyrifos. The revised assessment stated: "In light of the developing Agency policy on use of toxicology studies employing human subjects, HED [the Health Effects Division of EPA's Office of Pesticide Programs] selected doses and endpoints for risk assessment based solely on animal studies." At 2. The Agency derived from the animal data an acute NOAEL of 0.5 mg/kg/day and an acute LOAEL of 1.0. Although the animal study NOAEL and LOAEL were more than 10x higher than the human levels, because animal studies were used, the Agency applied an extra 10x inter-species uncertainty factor (UF) to calculate an acute dietary RfD of 0.005 mg/kg/day. This animal-based RfD was still higher than the previous 0.003 RfD based on human volunteer studies. However, the Agency's FQPA Safety Factor Committee of the HED decided that an additional 3x FQPA safety factor should be applied, resulting in a cumulative UF of 300 and reducing the RfD to 0.0017. Memorandum dated Oct. 14, 1999 from David Soderberg to Mark Hartman; Memorandum dated June 2, 1999 on "Replacement of Human Study Used in Risk Assessments" from Jess Rowland to Steve Knizner; Memorandum dated April 5, 1999 on "Report of the FQPA Safety Factor Committee" from Brenda Tarplee to Deborah Smegal. Subsequently, the Agency's Division Directors and senior scientists (DD-SS) overruled the FQPA Safety Factor Committee and "recommended that the FQPA safety factor should be **retained at 10X** for the protection of infants and children from

exposure to chlorpyrifos." Revised Risk Assessment at 3, original emphasis. Retention of the this FQPA 10x factor further reduced the acute RfD to 0.0005, in place of the previous RfD of 0.003.

6. Ethephon

Ethephon is an organic phosphorus compound used as a plant growth regulator due to its ethylene-releasing properties. It also has cholinesterase inhibiting effects. The online IRIS database RfD shows it was last revised on 03/01/1991. The RfD was set at 0.005 mg/kg/day, using a LEL of 0.5 mg/kg/day derived from a controlled human volunteer study. The study is cited as "Union Carbide Agricultural Products Company, Inc. 1977a. MRID 00066931." In that study, 10 humans were orally dosed at the 0.5 level for 16 days, followed by a recovery period of 29 days. The UF was set at 100 due to lack of a NOEL (i.e., 10x for lack of a NOEL, plus 10x for intra-species variability). The RfD determination also took into account as a non-principal study a human volunteer study ("Union Carbide, 1972) in which both males and females were given 1.8 mg/kg/day and a NOEL was not observed.

7. Ethion

Ethion is an organophosphate pesticide. EPA's online IRIS database shows that its oral RfD was last revised 09/01/1989. A NOEL of 0.05, and a LEL of 0.075, for plasma cholinesterase inhibition were based on a 21-day human volunteer study of 10 adult males. (Cited as FMC Corporation. 1970. MRID No. 00073157.) The RfD was also based on a subchronic (90-day) animal (dog) study showing inhibition of brain cholinesterase as a critical endpoint, with a NOEL of 0.06 mg/kg/day and a LEL of 0.71 mg/kg/day. An UF of 10 was used to account for intra-species variability in connection with the human data; and another 10x UF was added to account for the brain cholinesterase inhibition observed in the dog study. The RfD was set at 0.0005 mg/kg/day.

EPA issued a revised Human Health Risk Assessment for ethion on July 14, 1999. The revised risk assessment relied principally on animal studies, and the result was that the acute RfD was raised to 0.0017, while the chronic RfD remained at 0.0005. At 3. The risk assessment contains the following statement regarding the use of human test data:

> On July 27, 1998 the Agency announced that it is deeply concerned about the conduct of pesticide health effects [sic] on human subjects and that it would be consulting with its independent Science Advisory Board (SAB) about the application of stringent ethical standards to any such studies. The Agency further stated that no human studies of this type have been used by EPA for any final decisions about acceptable levels of pesticide under the new food safety law. Agency officials have stated that no final agency regulatory determinations will be

based on this kind of human study until the Agency has in place an approach for consideration of the ethical acceptability of any such study. At this time, the Agency has not yet received the response to its consultation with its scientific advisory committees and is continuing to work on its approach to these critical ethical questions.

During this period, EPA has continued to work through its risk assessment revisions and refinements for the organophosphates, including ethion, pursuant to the pilot process for public participation in risk assessment and risk management.

In previous assessments, reported in the Health Effects Division's Toxicity Endpoint Selection (TES) documents dated March 14, 1994 and October 10, 1995, the TES Committee based acute and chronic reference doses (RfDs), as well as occupational exposure and risk assessments, for ethion on a 21-day study conducted on human volunteers (MRID 00073157).

In light of the developing Agency policy on use of toxicology studies employing human subjects, and pending reassessment of this and other human studies for consideration of the ethical acceptability of such studies, HED has reconsidered the toxicology database for ethion and has for the acute dietary risk assessments, used a toxicology endpoint from an animal study and applied uncertainty factors informed by the existence of the human studies.

The standard uncertainty factor of 10 to account for interspecies extrapolation was reduced to 3. The intraspecies uncertainty factor of 10 was not reduced. Based on the NOAEL of 0.05 mg/kg/day established in an animal study, the acute dietary risk estimates do not exceed the Agency's level of concern for all populations, regardless of which interspecies factor was used (i.e., either 3 or 10).

All other risk assessments used only animal endpoints. OPP expects to reevaluate this acute dietary analysis pursuant to the Agency's decisions about how to consider the ethical acceptability of human studies and in light of the on-going efforts to develop peer-reviewed guidance for the scientific evaluation of any human studies that are determined to be ethically-appropriate for consideration in pesticide risk assessments.

At 2-3.

8. Malathion

The IRIS database shows that the oral RfD was last revised on 01/01/1992. At that time, the "principal study" supporting the RfD was a subchronic human volunteer feeding study, cited as "Moeller, H.C. and J.A. Rider, 1962. Plasma and red blood cell cholinesterase activity as indication of the threshold of incipient toxicity of ethyl-p-netrophenyl thiononobenzenephosphorate (EPN) and malathion in human beings. Toxicol. Appl. Pharmacol. 4:123-30." The study involved administering the chemical in gelatin capsules to five healthy

adult male volunteers for 32, 47, and 56 days at various doses. The study determined a NOEL of 0.23 mg/kg/day, and a LEL of 0.34 for RBC ChE depression. An uncertainty factor of 10 was used to arrive at the RfD of 0.02 mg/kg/day.

Malathion is currently undergoing a new review in connection with the FQPA review of organophosphates. Available materials are not clear on whether the human volunteer study previously regarded as the principal study is being considered; however, there are indications that it is not. A Dec. 22, 1998 memorandum, entitled "Malathion – Re-Evaluation", by the Health Effects Division's Hazard Identification Review Committee states in one place: "The HIARC concluded that even if the human study (where no females were used) had been chosen as the basis for the RfD, it would not be appropriate to apply additional uncertainty factor [sic] to account for the increased sensitivity of females as compared to males." At 16, underlining as in original.

9. Mercury and mercury compounds

EPA's IRIS oral RfD for methylmercury was last revised on 07/27/2001. Instead of employing a LOAEL/NOAEL approach, the RfD is based on a Benchmark Dose approach (BMD), with a "critical effect" of developmental neuropsychological impairment. While the "principal study" cited is a Faroe Islands epidemiologic study, employment of the BMD approach necessarily required dose conversion data, including data on human absorption, distribution, and excretion, and for these types of necessary data the Agency relied on at least five controlled human volunteer studies involving ingestion of fish contaminated with specific quantities of methymercury.

The methylmercury RfD summary shows that it relied substantially for its data on the Agency's mandated 1997 Mercury Study Report to Congress. (EPA-452/R-97-007, Dec. 1997.) That study also shows that substantial reliance was place on human volunteer studies for determining absorption and elimination rates in humans of elemental mercury, inorganic mercury, and methylmercury. *Id* at 2-1, 2-2, 2-3, 2-7, 2-8, 2-13, 2-14, 6-23, 6-24, 6-48, B-38, B-39 and B-43.

In January 2000, EPA issued final "Water Quality Criterion for the Protection of Human Health: Methylmercury". (EPA-823-R-01-001, Jan. 2001.) The criterion is not a binding regulation, but is intended to provide guidance to States and Tribes in setting water quality standards. (66 Fed.Reg. 1344 et seq., Jan. 8, 2001.) The criterion document states that it relies primarily on the information contained in the 1997 report to Congress, and briefly summarizes several human volunteer studies which provided human oral absorption and distribution data. *Id.* at 2-1 and 2-2.

10. Methyl parathion

The IRIS oral RfD was last revised 03/01/91. The RfD was based on a NOEL of 0.025 mg/kg/day observed in a 2-yr. rat feeding study. An uncertainty factor of 100 was applied to reach an RfD of 0.00025 mg/kg/day. Although treated as a "principal study", this rat feeding study was classified as only "supplementary". The portion of the RfD Summary under "Additional Studies/Comments" contains the following explanation regarding a human volunteer study for which only an abstract was available:

> In a subchronic study (30 days) with methylparathion in humans (Rider et al., 1971), RBC cholinesterase depression was reported, with a NOEL of approximately 0.3 mg/kg/day. Using a UF of 100 to adjust for chronic exposure and intraspecies sensitivity, an RfD based on this study would be 0.003 mg/kg/day. Adequate supporting data for human studies are not available. Nevertheless, even anecdotal data directly relating to human exposure should not be dismissed. Therefore, an RfD based on animal studies should not exceed 0.003 mg/kg/day unless additional data for humans can be found to support such a determination.

11. Nitrogen dioxide

EPA published a final rule on October 8, 1996 determining not to change the existing national ambient air quality standards for nitrogen dioxide. 61 Fed.Reg. 52852 et seq. The final rule relied on the health effects assessment presented in the Oct. 11, 1995 notice of proposed rulemaking. 60 Fed.Reg.52874 et seq. The standards decision relied substantially on human volunteer clinical studies of asthmatics (including adolescent asthmatics) for changes, and absence or reversibility of health effects, in pulmonary function or airway responsiveness. 60 Fed.Reg. at 52878, 52879 3d col. Additional information supporting the decision was presented in the 1993 "Air Quality Criteria for Oxides of Nitrogen" (EPA/600/8-91/049aF, Aug. 1993). The controlled human volunteer studies were discussed at 1-19 (Executive Summary), Chapter 15 (pp. 15-1 to 15-105 ("Controlled Human Exposure Studies of Nitrogen Oxides"), and Chapter 16, pp. 16-1 to 16-2 ("Health Effects Associated with Exposure to Nitrogen Dioxide", referring back to Chapter 15). The OAQPS Staff Paper supporting the decision not to revise the standard contains extensive discussion of the findings from the controlled human volunteer studies assessed in the Criteria Document. "Review of the National Ambient Air Quality Standards for Nitrogen Dioxide – Assessment of Scientific and Technical Information", pp. vii-viii, 16, 33-38, 43-46, 49-50, EPA-452/R-95-005, Sept. 1995.

12. Ozone

On July 18, 1997, EPA issued a final rule containing its decision to revise the national ambient air quality standard (NAAQS) for ozone and replace the 1-hr. standard with an 8-hr.

standard. 62 Fed.Reg. 38856 *et seq*. The decision was based substantially on controlled human studies of healthy and asthmatic subjects for lung function decrements, respiratory symptoms (e.g., cough, pain on deep inspiration), non-specific bronchial responsiveness, biochemical indicators of pulmonary inflammation, and exercise response. *Id*. at 38863-64, 38872, and 38873 and Criteria Document. Most, if not all, of the studies relied on were conducted by EPA. *Id*. at 38867. See also the Criteria Document at 1-23 to 1-26 (Executive Summary).

13. Pirimiphos-methyl

The IRIS database shows that the oral RfD was last revised 0l/01/1992. The principal studies supporting the RfD are two human volunteer feeding studies. One is a 56-day study with three males and four females, cited as ICI Americas Inc. 1976a. MRID No. 00080732; HED Doc. No. 005105. The other is 28-day feeding study with five males, cited as ICI Americas Inc. 1974a. MRID No. 00080747; HED Doc. No. 005105.

14. Sulphur dioxide

On May 22, 1996, EPA published a final decision not to revise the NAAQS for sulphur oxides. 61 Fed.Reg. 25566. The decision relies substantially on controlled human volunteer studies of mild, moderate, and moderate/severe asthmatic subjects exposed via mouthpiece or in chamber. Id. at 25570-73. Those studies are discussed in detail and evaluated in the *Supplement to the Second Addendum (1986) to Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982): Assessment of New Findings on Sulfur Dioxide Acute Exposure Health Effects in Asthmatic Individuals (1994)*(EPA-600/FP-93/002).

15. Zinc and zinc compounds (soluble salts)

The IRIS database shows that the oral RfD was last revised on 10/01/92. The RfD was based on a human clinical study which investigated the effects of oral zinc supplements on copper and iron balance in 18 healthy women over 10 weeks. (Yadrick et al., 1989.) The effects on copper and iron biochemistry are stated to be a concern because long-term iron or copper deficiency could result in significant adverse effects--for example, anemia and increased risk of coronary artery disease. The study found a LOAEL of 1.0 mg/kg/day, and did not determine a NOAEL. An uncertainty factor of 3 was used to arrive at an RfD of 0.3 mg/kg/day.