PPARα and Effects of TCE

We would like to offer a different opinion on the ideas presented in the article by Keshava and Caldwell (2006). The authors indicated that their article summarized scientific literature published since an earlier U.S. Environmental Protection Agency (EPA) risk assessment of trichloroethylene (TCE), with an emphasis on the possible role of proliferator-activated receptor α (PPARα) agonism relevant to TCE risk assessment. Interestingly, in the section on recent data on PPARα agonism, Keshava and Caldwell failed to establish any gene expression signature relating TCE and PPARα.

Keshava and Caldwell (2006) contended that it is difficult to identify a clear pattern of common gene expression changes for TCE and PPARα agonists in general. However, they did not consider numerous reports and reviews (e.g., Klaunig et al. 2003; Peters et al. 2005) illustrating that there are common and reproducible changes in gene expression associated with PPARα agonists. Further, extensive characterization has definitively demonstrated specific, direct targets of PPARα-retinoid X receptor heterodimers (reviewed by Klaunig et al. 2003). Keshava and Caldwell (2006) also did not discuss the possibility that the effect of TCE on gene expression could be mediated by mechanisms independent of PPARα, which likely explains the disparity described in their article. Keshava and Caldwell did not critically discuss the data summarized in their Table 2 (Keshava and Caldwell 2006), failing to note that many of these gene targets have no clear linkage with the PPARα agonist mode of action (MOA) and may be mediated either via different ligand–receptor–coactivator complexes that form on the promoter regions of the regulated genes by secondary events downstream of the initial events associated with PPARα activation, or by mechanisms that are independent of PPARα. In addition, the authors failed to describe the limitations of the various gene array platforms and to correctly interpret the findings in the context of gene targets by other PPARα agonists, especially when more comprehensive data sets exist but were not cited (Anderson et al. 2004a, 2004b).

Keshava and Caldwell (2006) further raised concerns regarding the use of PPARα-null mice to evaluate the MOA of PPARα by indicating that the physiologic differences observed in PPARα-null mice relative to wild-type mice suggest that the null mouse is an inadequate model to study the PPARα MOA. The data they cited, however, appears selective because they failed to mention that liver regeneration in PPARα-null mice is reportedly unchanged compared with wild-type mice (Rao et al. 2002), and age-related, sexually dimorphic obesity has not been observed in congenic PPARα-null mice (Akiyama et al. 2001). Thus, although the null mouse exhibits changes consistent with the critical role of PPARα in modulating fatty acid catabolism, this phenotype does not preclude its application for determining the critical role of this receptor in the MOA of PPARα agonists. Importantly, Keshava and Caldwell (2006) did not comprehensively discuss significant findings: a) that PPARα-null mice are refractory to liver tumors induced by two different PPARα agonists (Hays et al. 2005; Peters et al. 1997); b) that they are refractory to increased markers of replicative DNA synthesis and suppression of apoptosis after exposure to numerous PPARα ligands (summarized by Peters et al. 2005); or c) that PPARα-null mice expressing the human PPARα in the liver respond to PPARα agonists by increasing expression of genes encoding proteins that catabolize lipids, but they fail to show increases in markers of cell proliferation and are resistant to liver cancer (Cheung et al. 2004; Morimura et al. 2006). To dismiss these findings through lack of discussion or citation does little to advance our understanding and suggests that Keshava and Caldwell’s article is unbalanced.

Keshava and Caldwell (2006) also misrepresented an earlier review by Klaunig et al. (2003) regarding the MOA of PPARα agonists. Keshava and Caldwell (2006) incorrectly suggested that Klaunig et al. (2003) placed substantial weight on the associative event of peroxisome proliferation with this MOA, when, in fact, peroxisome proliferation was strongly—but not causally—associated, as noted for sustained increased cell proliferation. Keshava and Caldwell (2006) also misconstrued this review (Klaunig et al. 2003), focusing on DNA damage as a possible contributor to the MOA. Citing one manuscript that examined the effect of one, non-specific PPARα ligand (DHEA) is not sufficient to refute the comprehensive review by Klaunig et al. (2003). Finally, Keshava and Caldwell (2006) also suggested that the effects of PPARα ligands on mitochondrial function are part of the MOA, but they provided no direct evidence to support their contention that PPARα agonists or TCE causes mitochondrial dysfunction.

In summary, Keshava and Caldwell (2006) missed an excellent opportunity to critically and objectively examine the data that support or refute the role of PPARα in TCE-induced effects. In our opinion, their article did not advance our understanding of the MOA of PPARα agonists or TCE.

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. Consumer Product Safety Commission.

J.C.C. is employed by Pfizer, which is developing PPAR agonists for treatment of disease indications. R.M.D. is a member of the American Chemistry Council, Phthalate Esters Panel. J.G.D. is employed by Merck Research Laboratories, which has an interest in the development of PPAR agonists as therapeutic agents, and he owns stock and stock options in Merck. R.H.M. is employed by ExconMobil, a manufacturer of PPAR agonists (but not TCE). R.A.R. is employed by AstraZeneca, which has an active research program in PPARα agonists for potential treatment of lipid and glucose abnormalities associated with diabetes. The remaining authors declare they have no competing financial interests.

James E. Klaunig
Indiana University
Indianapolis, Indiana

Michael A. Babich
U.S. Consumer Product Safety Commission
Bethesda, Maryland

Jon C. Cook
Pfizer, Inc.
Groton, Connecticut

Raymond M. David
K&D Scientific Consulting Inc.
Pittsford, New York

John G. DeLuca
Merck Research Laboratories
West Point, Pennsylvania

Richard H. McKee
ExxonMobil Biomedical Sciences Inc.
Annandale, New Jersey

Jeffrey M. Peters
The Pennsylvania State University, University Park, Pennsylvania
E-mail: jmp21@psu.edu

Ruth A. Roberts
AstraZeneca UK
Macclesfield, Cheshire, United Kingdom

Penelope A. Fenner-Crisp
Consultant
North Garden, Virginia

REFERENCES
Akiyama TE, Nicol CJ, Fievet C, Staels B, Ward JM, Auwerx J, et al. 2001. Peroxisome proliferator-activated receptor-α regulates lipid homoeostasis, but is not associated with obesity: studies with conegenic mouse lines. J Biol Chem 276:39088–39093.
Anderson SP, Dunn C, Laughter A, Yoon L, Swanson C, Stulnig TM, et al. 2004a. Overlapping transcriptional
programs regulated by the nuclear receptors peroxisome proliferator-activated receptor alpha, retinoid X receptor, and liver X receptor in mouse liver. Mol Pharmacol 66:1440–1452.

Anderson SP, Howroyd P, Liu J, Qian X, Bahnemann R, Swanson C, et al. 2006. The transcriptional response to a peroxisome proliferator-activated receptor alpha agonist includes increased expression of protease maintenance genes. J Biol Chem 279:52389–52398.

Cheung C, Akiyama TE, Ward JM, Nicoll CJ, Feigenbaum L, Vinson C, et al. 2004. Diminished hepatocellular proliferation in mice humanized for the nuclear receptor peroxisome proliferator-activated receptor alpha. Cancer Res 64:3849–3854.

Hays T, Rusin I, Burns AM, Kenneth MJ, Ward JM, Gonzalez FJ, et al. 2005. Role of peroxisome proliferator-activated receptor-alpha (PPARalpha) in bezafibrate-induced hepatocarcinogenesis and cholestasis. Carcinogenesis 26:219–227.

Keshava N, Caldwell JC. 2006. Key issues in the role of peroxisome proliferator-activated receptor agonism and cell signaling in trichloroethylene toxicity. Environ Health Perspect 114:1484–1470; doi:10.1289/ehp.8993 [Online 9 May 2006].

Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, et al. 2002. PPARalpha agonist-induced rodent tumors: models of action and human relevance. Crit Rev Toxicol 33:655–780.

Morimura K, Cheung C, Ward JM, Reddy JK, Gonzalez FJ. 2006. Differential susceptibility of mice humanized for peroxisome proliferator-activated receptor-Wy-14,643-induced liver tumorigenesis. Carcinogenesis 27:1074–1080.

Peters JM, Cattley RC, Gonzalez FJ. 1997. Role of PPAR alpha in the mechanism of action of the nongenotoxic carcinogen and peroxisome proliferator Wy-14,643. Carcinogenesis 18:2029–2033.

Peters JM, Cheung C, Gonzalez FJ. 2005. Peroxisome proliferator-activated receptor-alpha and liver cancer: where do we stand? J Mol Med 83:774–785.

Rao MS, Peters JM, Gonzalez FJ, Reddy JK. 2002. Hepatic regeneration in peroxisome proliferator-activated receptor alpha-null mice after partial hepatectomy. Hepatol Res 22:52–57.

PPARα and TCE: Keshava et al. Respond

We appreciate the opportunity to discuss the issues raised by Klaunig et al. in their letter. First, we reiterate that, given the mini-mograph’s scope (Chiu et al. 2006), our article (Keshava and Caldwell 2006) was intended not to comprehensively review the role of peroxisome proliferator-activated receptor α (PPARα) agonism in trichloroethylene (TCE) toxicity but rather to “highlight some of the recently published literature on PPARα... to help inform and illustrate the key scientific issues relevant to TCE risk assessment.” In addition, we considered not just hepatocarcinogenesis, but a broader range of modes of action (MOAs) and toxicity effects, necessitating a brief discussion of the article by Klaunig et al. (2003). Furthermore, because of the pending National Academy of Sciences report and revision of the TCE assessment, Klaunig et al.’s suggestion to examine whether the data “support or refute the role of PPARα in TCE-induced effects” would have been premature in the mini-mograph.

In their letter, Klaunig et al. state that there are “common and reproducible changes in gene expression associated with PPARα agonists.” However, as described by Klaunig et al. (2003), the well-characterized changes are largely peroxisomal or related to lipid metabolism, and thus not related to hepatocarcinogenesis. Hays et al. (2005) and the Federal Insecticide, Fungicide, and Rodenticide Act Science Advisory Panel [FIFRA SAP (2004)] suggested that the MOA underlying PPARα agonist-induced hepatocarcinogenesis has not been fully elucidated in that the specific target genes modulated by PPARα leading ultimately to liver cancer have not been identified. We share the concerns of Klaunig et al. about critically interpreting gene array data and the concerns of Voss et al. (2006) about also considering dose-, time course-, species-, and strain-related differences. Given reports that PPARα agonists have zonal differences in hepatocyte, peroxisomal, and mitochondrial proliferation, and in foci development (Anderson et al. 2004a; Bannash 1996), zone-dependent and nonparenchymal cell responses (e.g., Kupffer cells) should also be taken into account. Finally, Table 2 of our article (Keshava and Caldwell 2006) illustrated the pleiotropic and varying liver responses of the PPARα receptor to various agonists, but we did not imply that these responses were responsible for carcinogenesis.

We agree with Klaunig et al. that PPARα-null mice have been useful in investigating the MOA for hepatocarcinogenesis, particularly for the strong agonist Wy-14,643 [(4-chloro-6-(2,3-xylyl)-2-pyrimidinyl]thio][acetic acid]. However, possible limitations of genetically modified mice, such as lack of complete tumor development or manipulation of the carcinogenic process, should be adequately characterized [U.S. Environmental Protection Agency (EPA) 2005]. Maronpot et al. (2004) noted the need for lifetime studies to characterize background or spontaneous tumor patterns and life spans (including those of the background strain) for these models.

PPARα-null mice have baseline differences from wild-type mice that may render them more susceptible to toxic responses [e.g., reduced glycogen stores, altered responses to fasting, elevated plasma free fatty acids, fatty liver, impaired gluconeogenesis, significant hepatic insulin resistance (Lewitt et al. 2001)], or potentially shorten their life spans with chemical exposure (Anderson et al. 2004b; Hays et al. 2005) or with further genetic modification (Nohammer et al. 2003). A comparison of their life spans with those of background strains without treatment has not been reported. Moreover, in PPARα-null mice, Wheeler et al. (2003) reported alteration of cyclin-dependent kinase/cyclin complexes necessary for cell cycle progression and DNA synthesis, whereas Voss et al. (2006) found increased apoptosis and decreased mitosis with fumonisin treatment. Thus, the question remains whether PPARα-null mice may have different susceptibility to hepatocarcinogenesis not specific to the proposed PPARα MOA.

Furthermore, bioassay study designs need adequate sensitivity to detect carcinogenic responses or elucidate MOAs. Morimura et al. (2006) and Hays et al. (2005) used high concentrations (with mortality), few (and differing numbers of) animals in treated versus control groups, and differing periods of exposure (all ≤ 1 year) complicating study interpretation. Interestingly, in the “humanized” PPARα-null mouse after 44 weeks of treatment, Morimura et al. (2006) noted (along with decreased toxicity) a Wy-14,643–induced adenoma resembling spontaneous tumors rather than those seen in PPARα agonist-treated wild-type mice; no tumors were observed in controls. This raises the question of whether, if tested for longer periods of time, the humanized mice might show significant responses with tumors more consistent with those induced by a variety of non-PPARα agonists and those observed in humans (Bannash 1996; Su and Bannash 2003).

We acknowledge the importance of Peters et al. (1997) demonstrating in vivo effects of Wy-14,643 on replicative DNA synthesis– and hepatocarcinogenesis–involved PPARα activation. Furthermore, we agree that peroxisome proliferation per se is an associative rather than causal event in the MOA for hepatocarcinogenesis (described by Rusyn et al. 2000). However, Klaunig et al. (2003) proposed a “minimal set of data elements” to support their PPARα MOA in rodents that consists of “PPARα agonism combined with light- or electron-microscopic evidence of peroxisome proliferation” or other markers of peroxisome proliferation. In addition, Klaunig et al.’s claim that we (Keshava and Caldwell 2006) misconstrued their review (Klaunig et al. 2003) as focusing on DNA damage as a possible contributor to the MOA is incorrect; that hypothesis was altered by Reddy and Rao (1989). We believe it is important to identify changes both specific to PPARα activation and related to carcinogenesis.

Voss et al. (2006) reported fumonisin-induced apoptosis, cell proliferation, gene changes, and liver lesions to be PPARα-independent but having some common target genes with PPARα agonists. Thus, we should not only understand a particular agent’s effects on the cell cycle and proliferation but also establish dependence on PPARα. Another issue is the applicability of
signalings on trichloroethylene toxicity. Environ Health Perspect. 114:1464–1470; doi:10.1289/ehp.8993 (Online 9 May 2006).
Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, et al. 2003. PPARα agonist-induced rodent tumor modulation: action and human relevance. Crit Rev Toxicol 33:655–780.
Kraupp-Grasl B, Huber W, Putz B, Gerbruch U, Schulte-Hermmann R. 1990. Tumor promotion by the peroxisome proliferator estrogen and inducing a specific subtype of altered foci in rat liver. Cancer Res 50:3701–3708.
Lewitt MS, Brismar K, Wang J, Virvill-Helferdy IL, Sindelar P, Gonzalez FJ, et al. 2001. Responses of insulin-like growth factor (IGF-I) and IGF-binding proteins to nutritional status in peroxisome proliferator-activated receptor α knockout mice. Growth Horm IGF Res 11:302–313.
Maronpot RR, Flacke G, Huff J. 2004. Relevance of animal cancer findings to human cancer prediction and prevention. Toxicol Pathol 32(suppl 1):46–48.
Marsman DS, Cattley RC, Conway JG, Popp JA. 1988. Relationship of hepatic peroxisome proliferation and replicative DNA synthesis to the hepatocarcinogenicity of the peroxisome proliferators di(2-ethylhexyl)phthalate and [4-chloro-6-(1,3-dimethyl)-2-pyrimidinyl]alanine acetate (WY-14,643) in rats. Cancer Res 48:6739–6744.
Morimura K, Cheung C, Ward JM, Reddy JK, Gonzalez FJ. 2006. Differential regulation of peroxisome proliferator-activated receptor α by WY-14,643 induced liver tumorigenesis. Carcinogenesis 27:1074–1080.
Nohammer C, Brunner F, Wolkart G, Stober PB, Steeyer E, Gonzalez FJ. 2006. Male infertility and mortality in peroxisome proliferator-activated receptor α knockout mice overexpressing lipoprotein lipase in muscle. Lab Invest 86:259–269.
Peters JM, Cattley RC, Gonzalez FJ. 1997. Role of PPAR α in the mechanism of action of the nongenotoxic carcinogen peroxisome proliferator-Wy-14,643. Carcinogenesis 18:2029–2033.
Reddy JK, Rao MS. 1989. Oxidative DNA damage caused by persistent peroxisome proliferation: its role in hepatocarcinogenesis. Mutat Res 214:63–68.
Rusyn I, Rose ML, Bojes HK, Thurman RG. 2000. Novel role of oxidants in the modification of action of peroxisome proliferators. Antioxid Redox Signal 2: 607–621.
Su Q, Bannansch P. 2003. Relevance of hepatic preneoplasia for human hepatocarcinogenesis. Toxicol Pathol 31:126–133.
U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001B. Washington, DC: U.S. Environmental Protection Agency.
U.S. EPA Science Advisory Board. 2006. SAB Review of EPA’s Draft Risk Assessment of Potential Human Health Effects Associated with PFFA and its Salts. EPA-SAB-06-006. Washington, DC:U.S. Environmental Protection Agency.
Voss KA, Riley R, Dunn C, Corton JC. 2006. The role of tumor necrosis factor alpha and the peroxisome proliferator-activated receptor alpha in modulating the effects of fumonisin in mouse liver. Toxicology. 222:165–174.
Wheeler MD, Smutney OM, Check JF, Rusyn I, Schulte-Hermmann R, Thurman RG. 2003. Impaired Ras membrane association and activation in PPARα knockout mice after partial hepatectomy. Am J Physiol Gastrointest Liver Physiol 284:O302–O312.

Aspartame Not Linked to Cancer

In an article published in the March 2006 issue of Environmental Health Perspectives (EHP) Soffritti et al. (2006) of the European Ramazzini Foundation of Oncology and Environmental Sciences (ERF) reported that aspartame was associated with an increase in lymphomas and leukemias, transitional cell carcinomas of the renal pelvis and urether, malignant schwannomas of peripheral nerves, and hyperplasia of the olfactory epithelium.

After the publication of the ERF aspartame study (Soffritti et al. 2006), the European Commission asked the European Food Safety Authority (EFSA) to assess the ERF aspartame carcinogenicity study results as a matter of high priority following the publication (EFSA 2005). The EFSA’s Scientific Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food (AFN, a 18-member panel that consisted of independent regulatory scientists and toxicologists, assessed the ERF aspartame carcinogenicity study using not only the ERF publication but also more extensive primary data and reports provided by ERF (EFSA 2006). Concurrently, the U.K. Food Standards Agency requested the opinion of the U.K. Committee on Carcinogenicity of Chemicals in Food, Consumer Products and Environment (COC) on the quality, analysis, and interpretation of the results of the ERF aspartame carcinogenicity study (Soffritti et al. 2006).

After a lengthy evaluation process, on 5 May 2006, the EFS published a 44-page report (EFSA 2006). A summary comment of the EFSA report on ERF study included the following:

The increased incidence of lymphomas/leukemias reported in treated rats was unrelated to aspartame, given the high background incidence of chronic inflammatory changes in the lungs and the lack of a positive dose–response relationship. … The slight increase in incidence of these tumours in rats fed aspartame is considered to be an incidental finding of the ERF study and can therefore be disregarded. (EFSA 2006)

The data on total malignant tumours do not provide evidence of a carcinogenic potential of aspartame. … [T]he aggregation of all malignant tumour incidences or all malignant tumour-bearing animals for statistical purposes is not justified, given that, as explained above, the lymphomas/leukemias and the renal tumours should have been excluded from the analysis. (EFSA 2006)

Concerning the malignant schwannomas, … the numbers of tumours were low, the dose–response relationship, while showing a positive statistical trend in males, was very flat over a wide dose range and there is also uncertainty about the diagnosis of these tumours. … [This finding can only be fully evaluated following a histopathological peer-review of all relevant slides related to the nervous system in the ERF study and if necessary also from the historical controls. (EFSA 2006)

Furthermore, the COC’s March 2006 minutes on the publication of the ERF aspartame study (Soffritti et al. 2006) concluded,
Aspartame: Soffritti Responds

As communicated in his letter, Abegaz represents Ajinomoto Corporate Services LLC. Ajinomoto, which holds 45% of the market share for worldwide aspartame production (Ajinomoto 2006), is well known for its aggressive and effective defense of its commercial interests. The action by Abegaz to reproduce portions of the opinion issued by the European Food Safety Authority (2006) regarding the results of our long-term carcinogenesis bioassay on aspartame (Soffritti et al. 2006) is clearly specious.

The author declares he has no competing financial interests.

Morando Soffritti
European Foundation of Oncology and Environmental Sciences “B. Ramazzini”
Cesare Maltoni Cancer Research Center
Bologna, Italy
E-mail: crcf@ramazzini.it

Children’s Health/Regional Collaboration to Reduce Lead Exposure in Children

As Safi et al. (2006) discussed, environmental contamination does not stop at international boundaries. An excellent example of a collaborative effort to address regional environmental exposures is that of the public health communities in Israel, Jordan, and the Palestinian Authority to assess and limit lead exposure of young children. Their dedication to this project in the face of significant political upheaval and episodic violence has demonstrated a remarkable commitment among international public health colleagues to improve environmental public health.

Safi et al. (2006) underscored the three most important strategies to prevent lead exposure in young children. First, eliminate leaded gasoline. In countries where this strategy has been successfully implemented, blood lead levels have significantly decreased (Pirkle et al. 1994; Schnass et al. 2004). More than 50 nations have eliminated lead in gasoline, and many others will initiate phase-outs over the next few years (Landrigan 2002).

Second, identify other consequential sources of lead and take action to control or eliminate them. Smelting remains a prevalent hazard in many parts of the world (ATSDR 1999). Efforts such as recycling batteries in controlled facilities have been successful in some countries.

Third, expand surveillance to ensure that recurrent or new sources of lead exposure are identified and that appropriate actions are taken. Both children and exposure sources travel. In the United States, we have found that the risk of lead exposure is much higher among immigrants when they arrive in the United States, usually as a result of use of lead-containing products; this elevated risk to the U.S. EPA for possible use in regulatory decisions, the rule also authorized an independent Human Subjects Review Board (HSRB) to evaluate these studies. How successful has the HSRB been?

The board’s first report (HSRB 2006), a scientific and ethical review of third-party,
intentional human-exposure studies on eight active ingredients used in pesticides, was issued 26 June 2006. The HSRB (2006) concluded that studies of seven pesticides [aldicarb, amitraz, azinphos-methyl, dichlorvos (DDVP), ethephon, methomyl, and oxamyl] “failed to fully meet the specific ethical standards prevalent at the time the research was conducted …” (see also Lockwood 2004; Needleman et al. 2005; Oleskey et al. 2004; Sass and Needleman 2004). Nevertheless, the HSRB (2006) concluded that

There was no clear and convincing evidence that the research [on these seven pesticides] was fundamentally unethical—intended to seriously harm participants or that informed consent was not obtained.

This second HSRB conclusion is ethically questionable on several grounds. First, it relies on an arbitrary definition of “fundamentally unethical” research as either intended to seriously harm participants or that fails to obtain informed consent. Yet neither the U.S. EPA (2006) nor the National Research Council (NRC 2004) defines “fundamentally unethical” so narrowly. Instead, both say only that studies which intend harm or violate consent are fundamentally unethical—intended to seriously harm participants or that informed consent was not obtained.

To assume that bad intentions are required to make serious harms fundamentally unethical also ignores “errors of omission” and focuses merely on commission—having harmful intent. Yet researchers err through omission if they behave irresponsibly toward their subjects: Perhaps they intend no harm, but through laziness, greed, or carelessness (Aristotle 1985), they fail to recognize subjects’ manifesting harmful symptoms.

The second HSRB conclusion also imposes an unfair burden on research victims or opponents, requiring them to establish researchers’ intentions. Yet intentions are almost impossible to know; they are private—not empirical—and thus typically known only by the individual. Proof of intent to harm is not required to judge bank robbers or white-collar criminals. Why should evaluators of research have such an unfair burden?

One reason for the HSRB’s questionable ethical conclusions may be inadequate bioethics expertise. No board members have terminal degrees in bioethics or even ethics. Fields represented are anesthesiology, environmental health sciences (2), epidemiology, medicine, microbiology, neurology, pharmacology (3), psychology, statistics (2), and toxicology (3) (HSRB 2006). The U.S. EPA also has not followed recommendations of its Science Advisory Board (2000), the NRC (2004), and the Environmental Medicine Workgroup (Oleskey et al. 2004) to establish specific ethics guidelines for all U.S. EPA-related research. Without such guidelines (e.g., avoid low-power studies), questionable ethical conclusions likely will continue.

The author declares she has no competing financial interests.

Kristin Shrader-Frechette
Department of Biological Sciences,
Department of Philosophy,
University of Notre Dame,
Notre Dame, Indiana
E-mail: kshrader@nd.edu

REFERENCES

Aristotle. 1985. Nicomachean Ethics (trans, Irwin T). Indianapolis, IN: Hackett.
Burton A. 2006. Human experimentation: a rule gone awry? Environ Health Perspect 114:A368–A363.
HSRB (Human Studies Review Board). 2006. April 4–6, 2000 Meeting EPA Human Studies Review Board Report.
Washington, DC: U.S. EPA. Available: http://www.epa.gov/OSA/hsrb/files/apr00bmtgfinalreport0606.pdf [accessed 15 September 2006].
Kant I. 1964. Groundwork of the Metaphysics of Morals. New York: Harper and Row.
Lockwood A. 2004. Human testing of pesticides. Am J Public Health 94:1908–1916.
Needleman H, Reigart JR, Landrigan P, Sass J, Bearer C. 2005. Benefits and risks of pesticide testing on humans [Letter]. Environ Health Perspect. 113:A804–A805.
NRC (National Research Council). 2004. Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues. Washington, DC: National Academy Press. Available: http://www.nap.edu/catalog/10927.html#toc [accessed 30 September 2006].
Oleskey C, Fleischman A, Goldman L, Hirschhorn K, Landrigan PJ, Lappe M, et al. 2004. Pesticide testing in humans: ethics and public policy. Environ Health Perspect 112:914–919.
Sass J, Needleman H. 2004. Industry testing of toxic pesticides on human subjects concluded “no effect,” despite the evidence [Letter]. Environ Health Perspect 112:A150–A151.
U.S. EPA. 2006. Protections for subjects in human research. Fed Reg 71:6137–6176. Available: http://www.epa.gov/fedrgstr/EPA-GENERAL/2006/February/Day-06/g01045.htm [accessed 30 September 2006].
U.S. EPA 2000. Comments on the Use of Data from the Testing of Human Subjects. A Report by the Science Advisory Board and the FIFRA Scientific Advisory Panel. EPA-SAB-EC-00-017 Washington, DC:U.S. Environmental Protection Agency. Available: http://www.epa.gov/science1/pdf/ex0017.pdf [accessed 30 September 2006].