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Via U.S. Mail and Facsimile [202-566-0255]
Information Quality Guidelines Staff
(Mail Code 2811R)
U.S. EPA
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Re: Information Quality Act Request for Correction - Guidelines for Carcinogen Risk Assessment, Basing Hazard Categorization on Results of Animal Studies

Dear Sir or Madam:

This is a Request for Correction (RFC) under the Information Quality Act (the "IQA"), Section 515 of Public Law 106-554, 44 U.S.C. § 3516, note; and the information quality guidelines issued by the Office of Management and Budget, 67 Fed. Reg. 8459-60 (Feb. 22, 2002) (the "OMB Quality Guidelines"), and by the Environmental Protection Agency, EPA/260R-02-008 (Oct. 2002) (the "EPA IQA Guidelines"). The RFC requests that EPA correct information contained in its Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001F (Mar. 2005). In particular, the RFC requests that EPA eliminate statements in the risk assessment guidelines that indicate that a substance may properly be labeled as "likely to be carcinogenic to humans" based solely or primarily on the results of animal studies. Such statements are scientifically unsound, an assessment shared by a majority of members of the Society of Toxicology nationwide. *See* Kraus, N., Malmfors, T., and Slovic, P. (1992), *Intuitive Toxicology: Expert and Lay Judgments of Chemical Risks Risk*, Risk Analysis 12:215-232. The Risk Assessment Guidelines' provisions regarding use of animal studies have led to numerous substances being deemed "likely" human carcinogens, despite the absence of evidence that the substances have caused *any* cancer in humans. The law permits EPA, if it so chooses, to adopt policies that err on the side of caution when faced with equivocal evidence regarding a substance's carcinogenicity; but the IQA does not permit EPA to distort the scientific evidence in furtherance of such policies.

Interests of Requesters

This RFC is being made by the Washington Legal Foundation ("WLF") and the American Council on Science and Health ("ACSH"). WLF is a public interest law and policy center based in Washington, DC, with supporters in all 50 states. WLF devotes a significant portion of its resources to ensuring that public policy decisions are based on the sound application of scientific

principles. In particular, WLF has regularly litigated in support of evidentiary rules that would exclude "junk" science from judicial proceedings. *See, e.g., Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999); *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579 (1993). WLF has litigated against broad application of the "Delaney Clause," a federal statute that bans from the food supply certain chemicals shown to cause cancer in animals. *See, e.g., Les v. Reilly,* 968 F.2d 985 (9th Cir. 1992), *cert. denied,* 507 U.S. 950 (1993). WLF represented Washington apple growers in litigation over false statements made by the national news media regarding cancer risks allegedly associated with use of Alar, a growth regulator applied to apples for several decades prior to 1989. *Auvil v. CBS "60 Minutes,"* 67 F.3d 816 (9th Cir. 1995), *cert. denied,* 517 U.S. 1167 (1996).

ACSH is a consumer education consortium concerned with issues related to food, nutrition, chemicals, pharmaceuticals, lifestyle, the environment, and health. ACSH was founded in 1978 by a group of scientists who had become concerned that many important public policies related to health and the environment did not have a sound scientific basis. These scientists created the organization to add reason and balance to debates about public health issues and bring common sense views to the public. With these goals in mind, ACSH produces a wide range of publications including peer-reviewed reports on important health and environmental topics. ACSH representatives appear regularly on television and radio, in public debates, and in other forums. ACSH is an independent, nonprofit, tax-exempt organization.

In January 2005, ACSH published *America's War on "Carcinogens": Reassessing the Use of Animals Tests to Predict Human Cancer Risk*, a book edited by ACSH's Elizabeth M. Whelan, Gilbert L. Ross, and Aubrey N. Stimola. The book concludes that efforts to use high-dose animal studies to characterize risks posed to humans by potential chemical carcinogens are badly flawed. The book concludes that such studies are often misinterpreted in a manner that distorts the risk to humans associated with exposure to such chemicals, confuses the public regarding which cancer risks matter most, wastes resources that could be more productively used in advancing public health, and (in some cases) actually undermines public health. More specifically, the book points out flaws in the manner in which EPA addresses the use of such animal studies.

EPA's Guidelines for Carcinogen Risk Assessment

EPA publishes and periodically revises a series of guidelines whose purpose is to assist risk assessors both within and outside EPA in evaluating the risks of environmental hazards. One of these documents specifically addresses the assessment of cancer risks: the Guidelines for Carcinogen Risk Assessment (the "Risk Assessment Guidelines"). These guidelines were most recently updated in final form in March 2005. EPA has stated that the guidelines are a work-in-

progress and that it "intends to revise" them when new scientific information warrants such revisions. Risk Assessment Guidelines at 1-2.

A principal focus of the guidelines is "hazard identification": can a chemical agent present a carcinogenic hazard to humans and, if so, under what circumstances? The guidelines direct investigators, after weighing all available evidence, to write a "weight of evidence" narrative that briefly summarizes the results of the hazard analysis and provides a conclusion with regard to human carcinogenic potential. The narrative is to express its conclusion using one of five "standard hazard descriptors": (1) "carcinogenic to humans"; (2) "likely to be carcinogenic to humans"; (3) "suggestive evidence of carcinogenic potential"; (4) "inadequate evidence to assess carcinogenic potential"; and (5) "not likely to be carcinogenic to humans." *Id.* at 1-11 to 1-12.

The guidelines include lengthy discussions regarding the use of animal studies in undertaking these hazard analyses. For example, in discussing conclusions that may be drawn from animal studies, the guidelines state, "In these cancer guidelines, tumors observed in animals are generally assumed to indicate that an agent may produce tumors in humans." *Id.* at 2-22. The guidelines state that an agent may be labeled "likely to be carcinogenic to humans" based on a variety of evidence derived from animal studies, including findings of: (1) an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans; (2) a positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy, or an early age at onset; (3) a rare animal tumor response in a single experiment that is assumed to be relevant to humans; or (4) a positive tumor study that is strengthened by other lines of evidence. *Id.* at 2-55.

Animal studies also play a prominent role in what the guidelines refer to as "default options." The guidelines recognize that there will be instances in which the scientific evidence regarding carcinogenicity is uncertain or absent; under those circumstances, the guidelines proscribe use of "default options" to supply otherwise unavailable answers. The guidelines state that since "[t]he primary goal of EPA actions is protection of human health," "the default options that are used in the absence of scientific data to the contrary, should be health protective." *Id.* at 1-7. Among the principal default options adopted by the guidelines is:

> [P]ositive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans. Thus, if no adequate human or mode of action data are present, positive effects in animal cancer studies are a basis for assessing the carcinogenic hazard to humans. This option is a public heath-protective policy, and it is both appropriate and necessary, given that we do not

test for carcinogenicity in humans.

Id. at A-3.

The use of default options also extends to the guidelines' discussion of mode of action.[1] The guidelines provide, "In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health-protective default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity." *Id.* at 1-10 to 1-11. Also, in determining whether there is a sufficient scientific basis for a finding of a mode of action for a substance, the guidelines direct investigators to make their determinations "in the context of science policy guidance" (*id.* at 2-42) – *i.e.,* when in doubt, err on the side of increased protection of public health.

Other Perspectives on the Use of Animal Studies

As the Risk Assessment Guidelines recognize, EPA's use of animal studies in predicting human cancer risks is controversial. *See id.* at A-3 ("The extent to which animal studies may yield false positive indications for humans is a matter of scientific debate."). A book recently published by ACSH, *America's War on "Carcinogens": Reassessing the Use of Animal Tests to Predict Human Cancer Risk* (hereinafter "*War on Carcinogens*"), presents a strong indictment of current federal policy regarding identification of human cancer risks. Because the book's findings are central to this RFC, we briefly summarize them here, particularly as they relate to the use of animal studies.

War on Carcinogens raises a warning flag regarding over-reliance on animal studies in predicting human cancer risk. It discusses at length the scientific evidence suggesting that not all substances that induce tumors in one species do so in others. Even when two species are closely related, for example mice and rats, numerous substances have been determined to be carcinogenic in one species but not the other. *War on Carcinogens* at 45. Many substances that cause cancer in rats have been determined not to cause cancer in humans. For example, while large doses of saccharin can cause bladder cancer in male rats, the mechanism that leads to such cancer is unique to male rats and has no relevance to humans. *Id.* at 46-47. Although FDA

[1] The guidelines define "mode of action" as "a sequence of key events and processes, starting with interaction of a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." *Id.* at 1-10 n.2. If the mode of action for a substance is well understood, then there generally will be scientific agreement regarding whether the substance poses a cancer risk for humans.

attempted to remove saccharin from the food supply in the 1970's, those efforts were abandoned in the 1990's once the mechanism by which saccharin causes cancer in male rats became known; indeed, in 2000 the National Toxicology Program removed saccharin altogether from the list of substances reasonably anticipated to be human carcinogens. *Id.* at 126-27.[2]

War on Carcinogens also addresses difficulties in extrapolating from the massive doses administered in animal studies to the far lower doses to which humans can expect to be exposed. Federal officials have generally adopted a linear model in assessing cancer risks -- the incidence of tumors is assumed to be directly proportional to dosage, and a substance determined to be carcinogenic at higher dosages is assumed to pose some risk no matter how small the dosage. *War on Carcinogens* points out that dose-response studies using laboratory animals have established that dose response generally are *not* linear and that small doses can often have absolutely no effect. *Id.* 51-54. The Risk Assessment Guidelines advise investigators to take steps to try to establish a dose response curve for each substance being investigated; however, where evidence is unavailable to establish such a curve, the guidelines mandate as a "public health-protective" default option that "cancer risks are assumed to conform with low dose linearity." Risk Assessment Guidelines at 1-10 to 1-11. *War on Carcinogens* points out that use of a linear model yields by far the highest estimate of risk and "can result in a gross overestimation of the low-dose risk." *War on Carcinogens* at 53.

War on Carcinogens goes on to challenge at length EPA's (as well as other federal agencies') basic premise that public health is protected when the government expends resources to limit individuals' exposure to substances that have even the slightest potential to cause cancer in humans. The book asserts:

> Overreliance on animal carcinogenicity testing as a predictor of human health has diverted both public attention and scarce economic resources from important and proven causes of cancer. In addition, it has sometimes led to the unnecessary replacement of useful and safe products with inferior and/or more costly

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[2] As the Risk Assessment Guidelines note, we do not perform tests for carcinogenicity in humans, and thus it is difficult to measure accurately the extent of the correlation between carcinogenicity in laboratory animals and carcinogenicity in humans. But as examples such as saccharin demonstrate, the correlation is far from exact. Indeed, the absence of epidemiological evidence that a substance causes cancer in humans is significant for any substance, such as saccharin, that has been regularly consumed by large numbers of humans over a long period of time. The saccharin example underscores the importance, when examining a substance for human carcinogenicity, of understanding the substance's mode of action and/or mechanism of action – an importance recognized by the guidelines.

alternatives.

Id. at 22. The book argues that the "war on carcinogens" is a "solution" in search of a problem: if one factors out illness caused by a few well-known causes of cancer (such as smoking cigarettes), there is no evidence that human cancer rates have risen in the past century due to increased exposure to synthetic chemicals, *id.* at 29-37; and "[i]n most instances, human exposure to trace levels of environmental chemicals pose negligible health risks." *Id.* at 23. Nonetheless, this RFC does not focus on those policy issues, but on the integrity of EPA's data. Regardless how one comes out on the underlying policy issues, the IQA requires EPA to maintain the scientific integrity of the information it maintains, and not to distort the information in the service of public policy goals.

The Information Quality Act

Adopted by Congress in 2000, the IQA is designed to "ensur[e] and maximiz[e] the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies." Pub. L. 106-554 § 1(a)(3), 114 Stat. 2763, *codified at* 44 U.S.C. § 3516 note. The IQA directs the Office of Management and Budget (OMB) to issue guidelines implementing the IQA; the OMB guidelines must in turn require every federal agency to which the guidelines apply (including EPA) to issue its own guidelines carrying out the goals of the IQA and to "establish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated that does not comply with the [OMB] guidelines." *Id.*, § (b)(2)(B).

The OMB Guidelines, issued in February 2002, require among other things that federal agencies "adopt specific standards of quality that are appropriate for the various categories of information they disseminate." *See* 67 Fed. Reg. 8452, 8458 (Feb. 22, 2002). In turn, EPA in October 2002 issued its own "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and the Integrity of Information Disseminated by the Environmental Protection Agency" [the "EPA IQA Guidelines"], EPA/260R-02-008. The EPA IQA Guidelines commit EPA to "the collection, generation, and dissemination of high quality information." *Id.* at 10. The guidelines define "quality" as including "objectivity," which according to the guidelines, "focuses on whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance is accurate, reliable, and unbiased." *Id.* at 15. When the information is deemed "influential" (as defined by § 6.2 of the guidelines), the guidelines hold EPA to a higher standard of quality. In pledging to meet that higher standard, the EPA IQA Guidelines state:

In our dissemination of influential scientific information regarding human health,

> safety or environmental risk assessments, EPA will ensure, to the extent practicable, and consistent with Agency statutes and existing legislative regulations, the objectivity of such information disseminated by the Agency by applying the following adaptation of the quality principles found in the Safe Drinking Water Act (SDWA) Amendments of 1996:
>
> (A) The substance of the information is accurate, reliable and unbiased. This involves the use of:
>
> (I) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and
>
> (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data).

Id. at 21-22 (footnote omitted).

WLF and ACSH respectfully submit that information contained in the Risk Assessment Guidelines, regarding the use of animal studies to assess whether substances under investigation are human carcinogens, complies with neither the OMB Guidelines nor the EPA IQA Guidelines. WLF and ACSH call on EPA to withdraw the offending information and to amend the Risk Assessment Guidelines so that they mandate that hazard and risk assessment be undertaken "in accordance with sound and objective scientific practices," not based on policy considerations divorced from the underlying science. Once scientifically defensible hazard and risk assessments have been undertaken, EPA (and other appropriate federal agencies) may well be statutorily empowered to apply policy preferences regarding regulation of the substances at issue, such as a "health-protective policy" of restricting access to substances for which there exists even a slight possibility of human carcinogenicity. What the OMB Guidelines and the EPA IQA Guidelines bar the agency from doing is to corrupt the scientific process by allowing extraneous policy consideration to color scientific fact-finding.

The Offending Passages Constitute "Information"

EPA cannot be heard to argue that because the Risk Assessment Guidelines is, in part, a policy document, the passages to which WLF and ACSH object do not constitute "information"

subject to the requirements of the EPA IQA Guidelines.[3] "Information" is broadly defined by the guidelines as "any communication or representation of knowledge such as facts or data, in any medium or form." *Id.* at 15. The guidance provided by the Risk Assessment Guidelines regarding when a substance should be deemed "carcinogenic to humans" or "likely to be carcinogenic to humans" fits comfortably within the term "knowledge such as facts or data."[4] The Risk Assessment Guidelines do not merely announce EPA policy regarding regulation of synthetic chemicals; rather, they purport to set forth EPA's knowledge regarding the quantum of scientific evidence necessary for one to conclude that a substance is carcinogenic, or likely to be carcinogenic, to humans.

The EPA IQA Guidelines provide numerous examples of items that EPA does not consider "information" within the meaning of the IQA. None of those examples are remotely similar to the objectionable provisions of the Risk Assessment Guidelines. Among the listed examples are: material on EPA's web site if it derives from outside sources and "is not adopted, endorsed, or used by EPA to support an Agency decision or position"; Internet hyperlinks; and "opinions, where EPA's presentation makes it clear that what is being offered is someone's opinion rather than fact or EPA's views." *Id.* at 15-16. Indeed, that final example strongly supports the view that the offending passages in the Risk Assessment Guidelines constitute "information" subject to the IQA: even if one were to argue that the offending passages should be deemed "opinion" rather than fact, there is no doubt that the opinions at issue constitute "EPA's views."

"Influential" Information Subject to Higher Standard of Quality

The OMB Guidelines direct federal agencies responsible for disseminating "influential scientific, financial, or statistical information" to take particular care to ensure the accuracy of that information, including the provision of a "high degree of transparency about data and methods to facilitate reproducibility of such information by qualified third parties." OMB Guidelines, 67 Fed. Reg. at 8460. There can be no question that the scientific information contained in the Risk Assessment Guidelines regarding the use of animal studies to determine human carcinogenicity qualifies as "influential" information.

The EPA IQA Guidelines deem information to be "influential" when "the Agency can reasonably determine that dissemination of the information will have or does have a clear and

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[3] The precise passages to which we object are set forth in detail *infra.*

[4] Moreover, there can be no question that the Risk Assessment Guidelines constituted "communication[s]" the moment they were released publicly in March 2005.

substantial impact (i.e., positive change or effect) on important public policies or private sector decisions." EPA IQA Guidelines at 19. Because the Risk Assessment Guidelines play such an important role in determining which substances will be labeled "carcinogenic to humans" or "likely to be carcinogenic to humans," and because those descriptors in turn play such a large role in important public policy and private-sector decisions, the information contained in the guidelines fits comfortably within the term "influential information." Indeed, the EPA IQA Guidelines state explicitly that information contained in top-level Agency documents, "i.e., rules, substantive notices, policy documents, studies, guidance," should be deemed "influential" information. *Id.* at 20. Moreover, the Risk Assessment Guidelines state that EPA "generally presumes" that "key cancer information" not only is "influential information" within the meaning of the EPA IQA Guidelines but also "highly influential" as defined by OMB. Risk Assessment Guidelines at 1-7.

Because information contained in the Risk Assessment Guidelines constitutes "influential" information, EPA is committed (as noted above) to adhering to particularly rigorous scientific standards in ensuring its reliability. That commitment includes a commitment to ensuring that "the substance of the information is accurate, reliable, and unbiased," including the use of "the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies." EPA IQA Guidelines at 22. By EPA's own admission, information contained in the Risk Assessment Guidelines falls far short of that standard. *See, e.g.*, Risk Assessment Guidelines at A-3 (EPA directs investigators to assume, under certain circumstances, that positive animal studies indicate that a substance is a likely human carcinogen, even though – as EPA admits – investigators may lack scientific data to support such an assumption).

Requested IQA Corrections

The stated purpose of the Risk Assessment Guidelines is to provide guidance for those assessing a substance's human carcinogenicity, to ensure that those investigators arrive at the most scientifically defensibly conclusions. Yet, throughout the Risk Assessment Guidelines is language that directs investigators, in certain instances, to be guided not by science, but by public policy concerns. Because all such language is scientifically indefensible due to its tendency to distort the scientific conclusions that would otherwise have been rendered, the Requestors ask EPA to comply with the IQA by deleting all such language. Policymakers may differ regarding the proper government response to scientific evidence concerning the degree to which a substance is likely to cause cancer in humans. But the policymaking process will be distorted unless policymakers are presented with an accurate assessment of the scientific evidence. The IQA was adopted to avoid such distortions; it requires that the Risk Assessment Guidelines be corrected to eliminate provisions that cause substances to be labeled "carcinogenic to humans" or

"likely to be carcinogenic to humans," despite the absence of evidence to support those labels.

WLF and ACSH do not mean to suggest that animal studies are not relevant to predictions of human carcinogenicity. To the contrary, in situations where good epidemiologic data are lacking, they are superior to any other available alternative. Not using animal studies in the safety evaluation of new substances to which humans will be exposed would subject humans to unnecessary risks. But it is widely understood within the scientific community that animal studies are far from perfect predictors of what will occur in humans. Thus, while evidence that a laboratory rat develops tumors when exposed to massive doses of a substance is certainly a basis for conducting further investigation, that evidence by itself comes nowhere near establishing that the substance is a human carcinogen. Yet, certain information contained in the Risk Assessment Guidelines inevitably has led and will lead to substances being labeled "likely" human carcinogens based on little more than a single positive animal study, in direct conflict with the IQA.

WLF and ACSH request that the following information in the Risk Assessment Guidelines be corrected:

* **Page 1-7.** The final sentence of the last complete paragraph reads as follows: "The primary goal of EPA actions is protection of human health; accordingly, as an agency policy, risk assessment procedures, including default options that are used in the absence of scientific data to the contrary, should be health protective (U.S. EPA, 1999b)." Everything following the semi-colon should be deleted and should be replaced by language similar to the following: "however, no risk assessment procedures should be employed unless they possess a sound scientific basis. In order to maintain their integrity as decision-making tools, risk assessments are not to be influenced by consideration of the Agency's health-protective goals."

* **Page 1-10 to 1-11.** The final sentence on Page 1-10 reads as follows: "In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity." This sentence should be deleted.

* **Page 1-14.** The final three sentences of the first paragraph read as follows: "In the absence of adequate human data for dose-response analysis, animal data are generally used. If there are sufficient quantitative data and adequate understanding of the carcinogenic process, a biologically based model may be developed to relate dose and

response data on an agent specific basis. Otherwise, as a default procedure, a standard model can be used to curve-fit the data." The third sentence should be deleted.

* **Page 2-22.** The first sentence of the first full paragraph reads as follows: "In these cancer guidelines, tumors observed in animals are generally assumed to indicate that an agent may produce tumors in humans." The sentence should be deleted and replaced with language similar to the following: "In these cancer guidelines, tumors observed in animals raise an inference that an agent may produce tumors in humans; but no assumption of human carcinogenicity is to be based on animal studies in the absence of substantial additional, credible scientific evidence supporting that assumption."

* **Page 2-42.** The fifth bullet point reads as follows: "Generally, 'sufficient' support [for making a mode of action determination] is a matter of scientific judgment in the context of the requirements of the decisionmaker or in the context of science policy guidance regarding a certain mode of action." The language following "requirements of the decisionmaker" should be eliminated.

* **Page A-3.** The first full paragraph begins as follows: "**Is the Presence or Absence of Effects Observed in an Animal Population Predictive of Effects in Exposed Humans?** *The default option is that positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans.* Thus, if no adequate human or mode of action data are present, positive effects in animal cancer studies are a basis for assessing the carcinogenic hazard to humans. This option is a public heath-protective policy, and it is both appropriate and necessary, given that we do not test for carcinogenicity in humans." This entire paragraph and the paragraph that follows should be deleted.

* **Page A-5.** The first full paragraph begins as follows: "*Target organ concordance is not a prerequisite for evaluating the implications of animal study results for humans.*" This entire paragraph and the paragraph that follows should be deleted.

* **Page A-10.** The first full paragraph begins as follows: "*Absent data to the contrary, the default assumption is that the cumulative dose received over a lifetime, expressed as a lifetime daily dose or lifetime average daily exposure, is an appropriate measure of dose or exposure.*" This entire paragraph should be deleted.

Basis for Correction

The EPA IQA Guidelines require EPA to ensure that "the substance of the information

[contained in the Risk Assessment Guidelines] is accurate, reliable, and unbiased," and that the Risk Assessment Guidelines employ "the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies." EPA IQA Guidelines at 22. Yet, EPA repeatedly states in the text of the Risk Assessment Guidelines that some of the scientific information contained therein is *not* based on the best available science but rather is based on EPA's views regarding good public health policy. Accordingly, EPA has essentially admitted that it is not in compliance with its own IQA guidelines; those require that the Risk Assessment Guidelines be amended to correct the scientifically inaccurate/unsupportable information. This is not to say that the Risk Assessment Guidelines may not adopt "default rules" that specify appropriate conclusions in the absence of adequate data; but the EPA IQA Guidelines require that all such default rules be based on sound science, not public policy considerations.

EPA's willingness to rely on "health-protective" public policy considerations in making hazard and risk assessments is particularly ironic, because in other contexts the Risk Assessment Guidelines decry resort to other public policy considerations. For example, the guidelines explain that the need for scientific "integrity" prohibit investigators from taking into account that a finding of human carcinogenicity could lead to regulatory action that would have severe social or economic consequences:

> Risk management applies directives in statutes, which may require consideration of potential risk or solely hazard or exposure potential, along with social, economic, technical, and other factors in decision making. Risk assessments may be used to support decisions, *but in order to maintain their integrity as decision-making tools,* they are not influenced by consideration of the social or economic consequences of regulatory action.

Risk Assessment Guidelines at 1-5 to 1-6 (emphasis added). For the same reasons that maintaining the integrity of risk assessments as decision-making tools requires that those scientific assessments not be biased by considerations of the social and economic consequences of regulatory action, the integrity of risk assessments requires that EPA not inject its health-protective policy judgments into the risk assessment process.

The guidelines seek to buttress their adoption of non-scientific default options (*i.e.*, default options based on a health-protective public policy) by pointing to NRC guidance. That reliance is wholly unpersuasive. The guidelines state:

> Use of health protective risk assessment procedures as described in these cancer guidelines means that estimates, while uncertain, are more likely to overstate than

> understate hazard and/or risk. NRC (1994) reaffirmed the use of default options as "a reasonable way to cope with uncertainty about the choice of appropriate models or theory" (p. 104). NRC saw the need to treat uncertainty in a predictable way that is "scientifically defensible, consistent with the agency's statutory mission, and responsive to the needs of decision-makers" (p. 86). The extent of health protection to the public ultimately depends upon what risk managers decide is the appropriate course of regulatory action.

Id. at 1-7 to 1-8. Contrary to EPA's claim, the NRC has never endorsed employing default options in the manner they are employed in the Risk Assessment Guidelines. The NRC explained that it makes eminent sense to adopt "scientifically defensible" default rules to "cope with uncertainty about the choice of appropriate models or theory" – thereby treating uncertainty in a predictable way. But it is no more "scientifically defensible" to base scientific conclusions on a health-protective public policy than it is to base those conclusions on the social or economic costs of potential regulations. EPA is correct that "the extent of health protection to the public ultimately depends upon what risk managers decide is the appropriate course of regulatory action"; but how can those risk managers be expected to make informed decisions when the EPA puts its thumb on the scale by incorporating unscientific health-protective public policy considerations into the risk assessment process?[5]

(1) The disputed language from Page 1-7 states explicitly that risk assessment procedures, including default options, should incorporate EPA's health-protective policy. The statement is a directive that, contrary to the IQA, requires investigators to base scientific determinations on non-scientific factors. The IQA requires correction of the information.

(2) The disputed language from Pages 1-10 to 1-11 adopts two "public health-protective" default options in the face of scientific uncertainty regarding a substance's mode of action: (1)

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[5] Moreover, it bears noting that there is considerable disagreement regarding what constitutes a "health-protective" policy. Implicit in the Risk Assessment Guidelines is an Agency assumption that it is always health-protective to err on the side of overstating a hazard or risk – thereby increasing the possibility that government regulators will take steps to reduce human exposure to the substance at issue. That assumption is far from self-evident. Many scientists believe that over-estimating cancer risks has a negative effect on public health. As *War on Carcinogens* points out, "Overreliance on animal carcinogenicity testing as a predictor of human health has diverted both public attention and scarce economic resources from important and proven causes of cancer. In addition, it has sometimes led to the unnecessary replacement of useful and safe products with inferior and/or more costly alternatives." *War on Carcinogens* at 22.

animal tumor findings are judged to be relevant to humans; and (2) cancer risks are assumed to conform with low dose linearity. The first default option is clearly designed to bias a hazard assessment in the direction of a finding that a substance is a human carcinogen. In a generalized sense, the sentence "animal tumor findings are judged to be relevant to humans" is largely unobjectionable, in that all scientists would agree that a substance that produces tumors in animals is more likely to be a human carcinogen than one that does not. But if that were all that EPA meant by the disputed language, there would be no reason to create this default option. Rather, in light of its context, the disputed language clearly conveys to investigators that – for public health-protective reasons – they should not hesitate to label a substance a "likely" human carcinogen if it produces animal tumors, regardless that there is insufficient scientific evidence to warrant any conclusions regarding mode of action (*i.e.,* scientists do not know what sequence of events might lead from human exposure to development of cancer). This first default option is scientifically unsound. Indeed, in a random survey of members of the Society of Toxicology, nearly three in five (58%) disagreed with the statement that "If a scientific study produces evidence that a chemical causes cancer in humans, then we can be reasonably sure that the chemical will cause cancer in humans." *War on Carcinogens* at 11 (citing N. Kraus, T. Malmfors, and P. Slovic (1992), *Intuitive Toxicology: Expert and Lay Judgments of Chemical Risks*. Risk Analysis 12:215-232.). If EPA really believed that its default option were scientifically defensible, it would have had no reason to defend the option as one based on a "public health-protective" rationale. The second default option (low-dose linearity) is also scientifically unjustifiable. Linear dose response curves "are not usually found experimentally in dose-response assays, and the idea that a dose response curve could take such a form is now considered obsolete." *Id.* at 52.[6] Adopting a low-dose linearity default option, in the absence of a scientific basis for doing so, "can result in a gross-overestimation of the low-dose risk." *Id.* at 53. The IQA requires correction of this scientifically unsound information by eliminating both default options.

(3) The disputed language from Page 1-14 states that, in the absence of "sufficient quantitative data and adequate understanding of the carcinogenic process, . . . as a default procedure, a standard model can be used to curve-fit the data" for purposes of undertaking a dose-response analysis – in other words, investigators may assume low-dose linearity. For all the reasons set forth above, such an assumption is scientifically unsound.

(4) The disputed language from Page 2-22 in essence creates a default option that

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[6] For example, "when the National Center for Toxicological Research conducted an extremely large (24,000-animal) dose response assay for mice using the potent carcinogen 2-acetylaminofluorene, which causes both bladder and liver tumors, they found that the dose-response relationships were nonlinear for both of these types of cancer." *Id.*

positive animal studies, standing alone, provide adequate justification for a conclusion that a substance is likely to be carcinogenic to humans. For all the reasons stated above, such a default option is scientifically unsound. The IQA requires correction of the information, to indicate that a positive animal study, standing alone, rarely or never provides adequate justification for a conclusion that a substance is likely to be carcinogenic to humans.

(5) The disputed language from Page 2-42 indicates that investigators, when making a mode-of-action determination, should take into account "science policy guidance" – *i.e.,* EPA's "public health-protective" policy should cause investigators to err on the side of determining, in close cases, that a mode of action (demonstrating how exposure can lead to human cancer) has been established. Because that information injects non-scientific considerations into the scientific fact-finding process, it violates the IQA and needs to be corrected.

(6) The disputed language from Page A-3 creates a default option that investigators may determine, based on a positive animal study, that a substance is a likely human carcinogen – even in the absence of any human or mode of action data. For all the reasons set forth in #2 above (regarding the language on Pages 1-10 to 1-11), the default option is scientifically unsound and thus violates the IQA. In support of its position, EPA argues, "The [default] option is supported by the fact that nearly all of the agents known to cause cancer in humans are carcinogenic in animals in tests that have adequate protocols." Risk Assessment Guidelines at A-3. EPA's conclusion simply does not follow from its premise. The fact that all dogs have four legs does not prove that all four-legged creatures are dogs. Indeed, as *War on Carcinogens* documents, the converse of EPA's statement is *not* true: "Most of the substances that have tested positive in animal carcinogenicity tests are of no known relevance to human cancer." *Id.* at 21. Moreover:

> A wide variety of naturally occurring food components have shown positive results in high-dose animal carcinogenicity tests. Except for mycotoxins, which are poisonous substances produced by molds and other fungi, however, few if any of these substances are believed to contribute to human cancer. Comparisons of substances using the Human Exposure/Rodent Potency (HERP) index indicate that the possible carcinogenic hazards posed by synthetic chemicals in the food supply are in the same range or lower than those posed by naturally occurring rodent carcinogens in ordinary foods.

Id. As noted above, saccharin is a well-known example of a substance that has shown positive results in high-dose animal carcinogenicity tests yet has been conclusively determined, based on mode-of-action and long-term epidemiologic studies, not to contribute to human cancer. *See id.* at 125-27. Accordingly, the fact that human carcinogens virtually always produce positive results in animal tests provides no sound scientific basis for adopting EPA's default option. The

default option is particularly problematic because it does not merely suggest that the "public health-protective policy" should be invoked in close cases to tip the balance in favor of a "likely human carcinogen" finding, but also appears to place the burden of proof on those who would deny the relevance of a positive animal study: "To demonstrate that a response in animals is not relevant to any human situation, adequate data to assess the relevancy issue are important." Because the disputed information injects non-scientific considerations into the scientific fact-finding process, it violates the IQA and needs to be corrected.

(7) The disputed language from Page A-5 creates, as a default option, that "target organ concordance is not a prerequisite" for invoking animal studies as a basis for finding that a substance is a human carcinogen. Yet, as EPA recognizes, "Target organs of carcinogenesis for agents that cause cancer in both animals and humans are most often concordant at one or more sites (Tomatis et al., 1989; Huff, 1994)." Risk Assessment Guidelines at A-5. EPA may well be correct that there are some exceptions to site concordance; accordingly, there would be scientific justification for including within the guidelines a statement that the absence of site concordance does not absolutely rule out a finding of human carcinogenicity. But by including this default option, EPA is strongly signaling to investigators that they should not attribute any substantial weight to the absence of site concordance. That signal is scientifically unsound, in light of the EPA admission cited above. The IQA requires that this information be corrected. If EPA is to include any default option at all, EPA should provide that, in the absence of scientific evidence that bears on the target organ concordance issue (*e.g.,* route of exposure, metabolism, mode of action), the default option is that positive animal studies regarding one organ do not support a finding of human carcinogenicity in a different organ.

(8) The disputed language from Page A-10 creates a default assumption that the cumulative dose received over a lifetime is an appropriate measure of dose or exposure. While EPA asserts that there is "some" empirical support for this default option, it admits that its position is adopted at least in part for "public-health-protective" reasons. *Id.* at A-10. Indeed, EPA cites to evidence suggesting that significant human exposure to a substance on one or two occasions can be far more dangerous than minute exposures over a longer period of time, even if the cumulative dose or exposure ends up being just as large in the latter situation. *Id.* The IQA requires that this information be corrected; any default option adopted by EPA must be solely a reflection of scientific judgment rather than being driven by a public health-protective policy.

How Requesters and Others Would Benefit from These Corrections

The goal of the Risk Assessment Guidelines is to accurately assess hazards and risks, not to protect public health. If the corrections requested by WLF and ACSH are made, both they and the public as a whole will benefit from the increased accuracy of hazard and risk assessments.

Those charged with developing public policy would benefit because they would have a better understanding of the health consequences of the regulatory actions they are considering.

Current and past versions of the Risk Assessment Guidelines, with their heavy reliance on animal studies and public policy-based default options, have led to numerous synthetic chemicals being labeled "carcinogenic to humans" or "likely to be carcinogenic to humans."[7] Those labels in turn have led public policy makers to impose substantial restrictions on use of the chemicals so labeled. Yet, with the exception of a few chemicals whose human carcinogenicity is well established, there is no evidence to suggest that those restrictions have led to any improvements in public health. Indeed, a comparison to the regulatory framework for naturally occurring substances strongly suggests that the manner by which EPA evaluates human cancer risks associated with synthetic chemicals is seriously flawed:

> [E]pidemiologic studies suggest that only a few naturally occurring carcinogens in foods – such as aflatoxins and substances in Chinese-style salted fish – play a significant role in the causation of human cancer. Yet toxicological studies indicate that large numbers of substances that test positive in animal carcinogenicity assays are naturally present in foods. . . The current double standard – by which synthetic substances are very tightly regulated while naturally occurring substances are virtually ignored – does not make scientific sense. The very fact that ordinary foods and naturally occurring food components would not pass the regulatory criteria used for synthetic chemicals indicates that something is amiss with the current system of evaluating carcinogenic hazards.

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[7] The large number of synthetic chemicals so labeled is a direct result of a surprising fact: a high percentage of all chemicals -- as high as 50% in some series -- test positive in animal carcinogenicity tests conducted at the maximum tolerated dose (MTD). *War on Carcinogens* at 146. The authors explain:

> As suggested by Bruce Ames, Lois Gold, and their colleagues (Gold et al, 2002), a likely explanation for many of these positive results is that toxicity at the MTD leads to increased cell turnover, which in turn increases the risk of cancer. In instances in which this is the only phenomenon contributing to the carcinogenicity of the substance and in which similar cell proliferation does not occur at lower doses, the applicability of results obtained at the MTD to lower, more realistic doses of the same substance is highly questionable.

Id.

War on Carcinogens at 146.

A current example of problems created by EPA's overreliance on animal studies involves perfluorooctanoic acid (PFOA), a chemical compound used to make Teflon. Rodents exposed to high doses of PFOA have developed several types of tumors. WLF and ACSH are unaware of any scientific evidence linking PFOA to human cancer; no mode of action has been established, and epidemiological studies indicate that workers who have had long-term exposure to PFOA do not face an increased cancer risk. Nonetheless, an EPA scientific advisory panel has recently recommended – based on the rodent studies – that PFOA be listed as a "likely" human carcinogen. Such a designation is sure to cause major economic disruptions and to lead to massive litigation, yet such a designation is foreseeable if the Risk Assessment Guidelines are applied as currently written. If the Risk Assessment Guidelines were corrected as suggested herein to comply with the IQA, the evidence publicly available to date suggests that PFOA would not be listed as a "likely" carcinogen.

These suggested changes would also benefit the public by focusing attention on those substances and lifestyles that genuinely pose a serious risk to public health. As things now stand, much of the public is convinced that "everything" causes cancer and thus there is little to be gained by avoiding cancer risks:

> False classification of a substance as a human carcinogen and failing to distinguish between true and trivial risks divert attention from important and proven causes of cancer. If chemicals continue to be classified as "probable human carcinogens" solely on the basis of limited animal test data, even if they pose negligible or no threat of human cancer, attention is drawn away from greater public health concerns. As the adage states, "when everything is dangerous, nothing is." When the word carcinogen is repeatedly used to designate anything and everything that causes cancer at high doses in laboratory animals, then the same word used in relation to observations in human populations loses its meaning (Whelan, 1992). People cannot – and should not be expected to – distinguish the few real hazards that are hidden in lengthy lists of hypothetical ones.

Id. at 139.

These suggested changes would also provide economic benefits to the public, if one assumes that corrections in the science will lead to changes in public policy. Resources are limited, and money that is spent on one project cannot be spent on something else. Environmental regulation and control of so-called toxic substances are expensive. The suggested

changes, by reducing public expenditures on regulatory programs designed to control substances no longer deemed toxic, would free public resources to address other, more pressing needs. *Id.* at 140-41. The suggested changes would also increase choices available to consumers by providing them with a wider variety of products. When products are taken off the market because of positive results in animal carcinogenicity tests, the alternative products that replace them may be less satisfactory, either in terms of safety or their ability to perform the functions for which they are intended. At the very least, substances that are banned are likely to be replaced with substances that are not as well understood as their predecessors were; in general, scientists and regulators almost always have more information about a chemical that is the target of regulatory action than about any available substitute. *Id.* at 141-42.

While WLF and ACSH hope that the requested changes in the Risk Assessment Guidelines would lead to changes in public policy with fewer restrictions being placed on substances posing nonexistent or trivial cancer risks, that is not the primary goal of this RFC. If they so choose, public policy makers would still be free to impose restrictions even on those synthetic chemicals determined – following correction of the guidelines – not to be "likely" human carcinogens but merely to present "suggestive" or "inadequate" evidence of carcinogenicity. But the IQA demands that public policy makers be permitted to make those

choices based on "the best available science." EPA IQA Guidelines at 22. The corrections requested herein would ensure that public policy makers receive sound scientific information regarding human cancer risks posed by a substance before they consider whether to impose restrictions on use the substance.

Respectfully submitted,

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