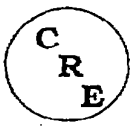

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March 3, 2004

Kerry Weems
Principal Deputy Assistant Secretary
for Budget, Technology and Finance
U.S. Department of Health and Human Services
200 Independence Ave., SW
Hubert Humphrey Bldg., Rm. 514G
Washington, DC 20201

Dear Mr. Weems:

We are recommending that HHS and NIH add the Report on Carcinogens (RoC) program to the list of programs in the FY 2007 NIH budget which will be evaluated by HHS/NIH and OMB with the Program Assessment Rating Tool (PART).

The RoC program is administered by the National Institute of Environmental Health Sciences (NIEHS) and the other federal agencies which participate in the National Toxicology Program (NTP).

The principal mission of NIH and the NTP is health research.[1] The RoC program is not a research program, and it competes for resources for that principal mission; therefore issues concerning its justification should be given serious attention. The scientific community and RoC stakeholders, including government agencies with related programs, have raised serious and legitimate issues regarding the usefulness of the RoC program and the manner in which it is administered. Those issues are discussed below in connection with specific PART questions.

Although the RoC program is Congressionally mandated, it is still subject to PART evaluation and budget justification, as has been made clear by OMB.[2] This should be particularly true when many of the PART issues pertain substantially to whether the program is being conducted in accordance with Congressional intent.

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[1] Research is also a basic strategic goal of HHS. Goal 4 of the HHS Strategic Plan for FY 2004-09 is "Enhance the capacity and productivity of the nation's health research enterprise." The use of HHS funds for the RoC program impacts that goal.

[2] OMB's Frequently Asked Questions on PART, number 32, specifically addresses programs mandated by statute, stating: "If statutory provisions impede effectiveness – for example, if resources are not targeted effectively or spread too thinly to have an impact – one result of a PART review may be recommendations for legislative changes."

Brief General Background on the RoC Program

Preparation of the RoCs was mandated by Congress in 1978 as a small part of large public health legislation.[3] The RoCs provide lists of substances or agents which have been determined by HHS to be "known human carcinogens" or "reasonably anticipated human carcinogens", along with a summary of the scientific information supporting the determination and information on exposure sources. The statute also requires the RoCs to provide an evaluation of the efficacy of any current regulatory standards; however, as discussed below, that portion of the mandate has not been followed.

Initially, the legislation required a report every year; in 1993 that was changed to every two years. HHS is currently about to publish the 11th RoC, and it has begun work on the 12th RoC by announcing 21 new nominations for listing, and by soliciting public comments on each.

Each nomination of a substance or agent for listing in the RoCs requires preparation of a detailed "background document" by expert outside consultants and NIEHS staff, review by four separate committees, and extensive public comments, before the Director and the Secretary make a listing decision for publication in the next edition of the RoC.[4]

While the RoC program is administered by NIEHS under delegation from the Secretary of HHS, the RoC program has an inter-agency dimension as part of the National Toxicology Program.[5] The NTP "core" agencies are all HHS agencies -- NIEHS, NIOSH (part of CDC), and NCTR (the National Center for Toxicological Research, which is part of FDA) – and a number of non-core agencies participate through membership on the NTP Executive Committee and the NTP Board of Scientific Counselors. Those non-core agencies are ATSDR (HHS), CPSC, EPA, NCEH (CDC), NCI (NIH), NIH, and OSHA (Dept of Labor).

Several public reviews of the RoC program have been conducted – in 1994-96, 1999, and 2004 – however, those reviews have addressed mainly issues of stakeholder input and the listing criteria, not the PART questions discussed below.

To the best of our knowledge, there has been no Congressional oversight or GAO review of the RoC program since the original legislation in 1978.

The following OMB PART questions are clearly relevant to the RoC program and should, we believe, be addressed in connection with the FY 2007 NIH budget justification and performance plan. The specific PART questions below are taken directly from the OMB PART guidance.

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[3] 42 U.S.C. §241(b)(4).

[4] The listing review procedures are explained on the RoC portion of the NTP website.

[5] The Director of NIEHS is also Director of the NTP. Administration of the RoC program by the Director affects his or her ability to focus on the research aspects of the NTP.

It also appears that NIEHS fails to consult with other federal agencies prior to nominating substances for listing in the RoCs, thus leading to the sort of situations described above with regard to asphalt fumes and atrazine.

1.5: "Is the program design effectively targeted, so that resources will reach intended beneficiaries and/or otherwise address the program's purpose directly?"

This has been addressed above. The RoC program does not have a defined target, and it is not targeted to provide sound information to the American public, as Congress intended.

3.5: "Does the program collaborate and coordinate effectively with related programs?"

Assuming "related programs" includes programs by other Federal agencies and State and international health and science organizations to evaluate substances for carcinogenicity and regulate exposure, the RoC program does not collaborate and coordinate effectively. This is shown by the controversy involved in the recent nominations of atrazine and asphalt fumes for listing in the 12th RoC, as discussed above (under 1.3). Whatever formal collaboration and coordination with other federal agencies occurs during the RoC program does not occur until the NTP Executive Committee meets to review individual nominations. Since the review by the NTP Executive Committee is the fourth committee review in the RoC review process, nominations have usually acquired too much momentum by that point for the Executive Committee to conduct an impartial evaluation. In addition, NIEHS recently announced, in its response to public comments from its 2004 process review, that the NTP Executive Committee reviews only RoC "policy" issues.

4.4: "Does the performance of this program compare favorably to other programs, including government, private, etc., with similar purpose and goals?"

Assuming performance is measured in terms of the Congressional intent, which was that the RoCs should disseminate useful risk information to the American public, the RoC program, by its own admission, does not produce any performance results. Programs of other federal agencies arguably provide far more useful performance results by providing risk information; however, even that risk information is usually not objective scientific information because the scientific data are intermixed with policy-driven assumptions (*i.e.*, allegedly health-protective precautionary assumptions) in such a way that they cannot be disentangled. The RoCs could provide superior information by providing objective information on levels of exposure at which substances are "known" or "reasonably expected" to cause cancer, but they do not do so.

4.5: "Do independent evaluations of sufficient scope and quality indicate that the program is effective and achieving results?"

Since federal regulatory agencies evaluate the same substances for carcinogenicity and promulgate exposure standards, and since the RoCs do not evaluate the efficacy of those standards as mandated by Congress, it appears impossible to determine whether the RoCs are producing any of the results intended by Congress beyond those produced by the regulatory agencies.

prominent toxicologists wrote to Secretary Shalala in 1999 to point out that the RoCs are confusing and ineffective because they do not provide to the public the crucial information on the level of exposure to a particular substance or agent which is "known" or "reasonably anticipated" to cause cancer. They also questioned whether this absence of useful information was intended by Congress, and whether the resources currently devoted to preparing the RoCs might be better invested in basic health research. A copy of this 1999 letter to Secretary Shalala is attached. The issue had also been raised earlier in July 1999 by members of the scientific community attending The Toxicology Forum in Aspen, CO at which the subject was on the agenda and the NTP Director and RoC staff were present to hear comments.

Stakeholders also raised the issue during the 1999 review, and during the 2004 review as well. Nevertheless, NIEHS has never responded by addressing the legislative intent, and has only stated that it believes the RoC background documents provide sufficient information on exposure and dose. Since the background documents are not part of the RoCs, and it is very unlikely that they are read by members of the general public, this is not an adequate response.[8]

In addition, the 1978 Congressional mandates require that the RoCs provide information on the extent to which any current federal regulatory standards reduce risk, but the RoCs fail to do this. They only present information on the standards themselves, not the extent to which they reduce risk.

The standard Introduction to the RoCs indicates that this failure to provide relevant information on exposure or dose and the efficacy of regulations is not based on considerations regarding utility or science, but rather on policy assumptions. The Introduction states, in essence, that the Agency has adopted the assumption that any reduction in exposure will decrease the incidence of cancer, and that this assumption is "the basis of current regulatory policies" employed throughout the federal government.[9] Such a statement is not only a policy-based, rather than scientific, statement, but is also clearly inaccurate. Current regulatory policy is based on attempting to determine levels of exposure which are considered "safe". The stated assumption on which the RoCs are based is reflective of the old "Delaney Clause" regulatory approach, which was repealed by Congress when it enacted the Food Quality Protection Act in 1996.

A review of the legislative history, which has consistently been avoided by the Agency, shows that Congress intended that the RoC's provide useful "risk" information to the public which they could employ in their daily lives, directly contrary to the approach adopted by the Agency.

The 1978 House report on the original legislation for the RoC contains the following

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[8] Stakeholders have also raised the issue that the listing criteria for the "known" category are unclear, both as interpreted by the agency and as actually applied to certain substances, such as dioxin . We have not addressed that issue in this letter, since it is not primarily a PART issue, although it does pertain to the effectiveness of the RoC program.

[9] Introduction to the 11th RoC at p. 4.

statements.[10] (There was nothing pertaining to the RoC legislation in the Senate report.)

- The Reports "must include . . . an evaluation of the efficacy of existing regulatory standards designed to reduce or eliminate exposure to carcinogens." At 22. This could not be done without an evaluation of the level of exposure known or reasonably anticipated to cause cancer. This directive is also contained in the plain language of the statute. The RoCs do not do this.

- "If an individual recognizes a substance on the list to which he or she suspects that significant exposure occurred, then measures could be taken though medical examination or other screening procedures to detect cancers before they become malignant." *Id.* (emphasis added). Presumably, Congress meant that the public could gauge the significance of their exposure based on information provided in the RoCs on the levels of exposure known or reasonably anticipated to cause cancer.

- "The relative toxicity of such agents should be described, to the extent such information is known . . . the levels of exposure to be expected from certain occupations, geographic areas, foods or consumer goods, and the identification of subpopulations expected to be at higher than average risk (for example . . .)." At 28 (emphasis added). Toxicity is a function of the level of exposure (or dose – internal exposure). Obviously, higher than average risk cannot be ascertained unless the RoCs assess an average level of risk, which they do not, since they only provide "hazard" information (i.e., whether there is a danger at some level of exposure, which, as studied, might be a level orders of magnitude higher than an average level of exposure).

On the floor of the House, Congressman Rogers, Chair of the Subcommittee on Health and Environment, where the RoC legislation had originated, further explained the intent behind the legislation on behalf of the full Committee on Commerce:

> It is the committee's intent that any such list [the RoC listings] include . . . any uncertainties in the data yet to be resolved, and where possible, estimates the [sic] magnitude of the risk each [substance, etc.] poses. . . . Information concerning the relative risk posed by each substance and the quality of data will be made unequivocably [sic] clear to the reader."

Cong. Rec., Oct. 10, 1978, 34938 (emphasis added). The RoCs do not provide any information on the magnitude of risk or relative risk.

Mr. Rogers' explanation was the only explanation made during floor consideration before passage.

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[10] H.R. Rep. No. 1192, 95th Cong., 2d Sess., 22-23, 28, 45 (May 15, 1978).

The joint House-Senate explanation of the legislation reflects that the final legislation was based on the House bill, since the Senate bill contained no comparable provisions. Cong. Rec., Oct. 14, 1978, 38653, 38657-58.

It therefore appears that the RoC program is currently being conducted in a manner contrary to Congressional intent and so that it lacks the utility to the public that was intended by Congress.

1.2: "Does the program address a specific and existing problem, interest, or need?"

Cancer is certainly a problem, but the RoCs do not "address" that problem in a meaningful way, as intended by Congress.

1.3: "Is the program designed so that it is not redundant or duplicative of any other Federal, State, local or private effort?"

Numerous other federal agencies (such as EPA, OSHA, FDA, ATSDR, and CPSC), as well as State and international agencies[11], conduct risk assessments for the same substances as are listed in the RoCs, and many of them have promulgated regulatory standards, guidance levels, bans, or labeling requirements based on that risk information. The type of "hazard" information contained in the RoC listings is routinely supplied as a part of those risk assessments. The RoCs provide hazard information which is redundant and duplicative of the hazard information contained in, or underlying, those risk assessments conducted by other agencies under other programs.

The cancer risk assessments conducted by regulatory agencies usually result in quantitative estimates of risk which are based to a significant degree on assumptions rather than scientific knowledge, including significant assumptions which are policy-driven. Examples would include the assumption of low-dose linearity of dose-response for putative carcinogens and the resolution of inconsistent data or data gaps by selecting "conservative" (*i.e.*, presumably more health-protective) data as the determinative data. The RoCs could avoid redundancy and duplication by providing basic factual information which has not been influenced by policy and which does not purport to determine a specific numerical estimate of risk at a certain exposure level (for example, a risk of 3×10^{-5} at an exposure level of 6 parts per billion). They could do this by simply stating factually the exposure levels at which studies have shown there is a causal relationship with cancer, or at which it appears it is credible that there is a causal relationship. As the Agency itself has already pointed out, such information is contained in the background documents, so that incorporating it into the RoC listing information would not involve any significant extra effort.

It should be pointed out that the RoCs are not only duplicative and redundant[12], they also

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[11] The listings and information in the RoCs large duplicate the listings and information provided by the cancer monographs produced by the WHO's International Agency for Research on Cancer ("IARC"). Scientists from U.S. federal agencies frequently participate in preparing the IARC monographs.

[12] Another example of potential duplication is the petition currently pending before FDA to require a cancer warning label on cosmetics containing talc. NIEHS recently nominated cosmetic talc for listing in the 12th RoC.

sometimes conflict with information provided by other federal agencies. For example –

- The RoCs list "Alcoholic Beverage Consumption" as a "known human carcinogen".[13] At the same time, the Dietary Guidelines for Americans, produced jointly by HHS and USDA, inform the public that moderate consumption of alcoholic beverages is not harmful, and a label for alcoholic beverages mandated by the Bureau of Alcohol, Tobacco, and Firearms refers the public to the Dietary Guidelines.

- After the 9th RoC listed 2,3,7,8-TCDD (often referred to as "dioxin" or TCDD) as a known human carcinogen (based on studies of humans highly exposed as a result of industrial accidents, as well as animal and *in vitro* data), EPA also proposed to classify TCDD as a known human carcinogen, but a majority of its Science Advisory Board disagreed, and the National Academies are now conducting a study on the possible risks of TCDD.

- NIEHS has nominated the widely-used herbicide atrazine for listing in the 12th RoC. EPA has objected to the nomination in a public comment letter (posted on the NTP website) because EPA and its Scientific Advisory Panel had just completed an intensive review of atrazine and had decided that it was not carcingenic. The EPA letter states that "the effort proposed by NTP [to review atrazine for possible listing in the 12th RoC] would be duplicative of work already performed by EPA, as well as work EPA has committed to perform in the future."

- In the late 1990s, NIOSH and the Interagency Committee on Chemical Evaluation and Coordination decided that additional studies of asphalt fumes were needed in order to make a determination of carcinogenicity. This decision was concurred in by other agencies such as WHO and Cal/OSHA. The recommended studies are currently under way. Nevertheless, this year NIEHS nominated asphalt fumes for listing in the 12th RoC.

1.4: "Is the program design free of major flaws that would limit the program's effectiveness or efficiency?"

The failure of the RoCs to provide the public with information on the levels of exposure which are "known" or "reasonably anticipated" to cause cancer is such a major flaw, and it renders the RoCs essentially useless and misleading to the public.

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[13] At the insistence of its external peer review committee, the Agency included in the listing information the statement that "[s]tudies indicate that the risk of cancer is most pronounced among smokers and at the highest levels of consumption." This may be the only reference to risk and exposure levels throughout the RoCs. Nevertheless, it still indicates that alcoholic beverages are known to cause cancer at any (low) level of consumption, which is inaccurate and misleading.

Our review of these PART questions as applied to the RoC Program, presented below, indicates that there are serious problems with the program and that it is difficult to justify continued funding.

OMB PART Questions Particularly Pertinent to the RoC Program

1.1: "Is the program purpose clear?"

This is perhaps the central question. For a long time the RoCs have been regarded as very puzzling in this regard. In their Introductions, at the very outset, the RoCs state that each edition is "an informational scientific and public health document" that "serves as a meaningful and useful compilation of data on [carcinogenicity of various substances and agents]." However, immediately following this statement is another, contradictory, statement that "[l]isting of substances in the RoC . . . does not establish that these substances present carcinogenic risks to individuals in their daily lives." In other words, the RoCs do not provide information on carcinogenicity that is useful to the public, but they nevertheless claim to be a "meaningful and useful" scientific and public health document. The program purpose is therefore not clear.

A review of the listing information provided by the RoCs will quickly show that data critical to making the RoCs an accurate and useful public health document are missing. The RoCs do not provide the critical data on the level of exposure at which a substance is "known" to cause cancer or "reasonably anticipated" to cause cancer. Instead, the RoC listings provide only "hazard" information, rather than "risk" information, and thereby indicate to the public that any degree of exposure to the substance is "known" or "reasonably anticipated" to cause cancer.[6] Such an approach is not regarded as scientifically valid and useful by the scientific community, and other federal public health agencies provide the public with "risk" information and use "hazard" information as only a preliminary screening tool in the risk evaluation process. By failing to provide information on levels of exposure or dose "known" or "reasonably anticipated" to cause cancer, the RoCs not only lack utility, they are also likely to be misleading to the public.[7]

During the public review process of the RoC program in 1999 this problem with the RoCs was pointed out by members of the scientific community and stakeholders. For example, eleven

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[6] "Hazard" information is information which indicates that a substance is dangerous at some level of exposure and dose -- levels which might have little or no relevance to the public because the danger was observed in connection with industrial accidents or worker exposures that occurred far in the past but which are no longer allowed. "Risk" information indicates the level of danger at a particular level or exposure or dose, and is usually used to determine a level of exposure which is "safe" or which presents an insignificant risk.

[7] Information disseminated to the public which lacks "utility" violates the Data Quality Act and its implementing guidelines. 44 U.S.C. § 3516, note; 67 FR 8452, 8459, Feb. 22, 2002 (OMB guidelines for federal agencies – the HHS guidelines conform to the OMB guidelines with regard to the "utility" requirement).

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Conclusions and Recommendations

The RoC program as currently conducted does not carry out the Congressional intent for the program and is not effective in providing useful information. Continued funding of the RoC program detracts from the resources available for funding of HHS and NIH research, and therefore its justification should be carefully examined. The PART was created for just such an evaluation, and numerous PART questions are applicable to the RoC program. We recommend that the PART therefore be employed as intended to evaluate the Report on Carcinogens program.

Thank you for your consideration of this recommendation. We would appreciate knowing whether the Agency will adopt this recommendation.

Sincerely,

William G. Kelly, Jr.
CRE Western Representative

Attachment

cc w. att: Bill Beldon, Deputy Assistant Secretary for Budget
Art French, Acting Director, Division of Budget Policy, Execution & Review

The University of Kansas Medical Center

School of Medicine
Department of Pharmacology,
Toxicology and Therapeutics

11 September 1999

The Honorable Donna E. Shalala
Secretary
Department of Health and Human Services
200 Independence Ave., SW
Washington, DC 20201

Dear Madam Secretary:

We understand that your Department is currently inviting public comment on issues associated with the biennial *Reports on Carcinogens*. As members of the medical and scientific communities, we are writing to express briefly our principal concerns.

The manner in which information is conveyed to the public through the *Reports* is confusing. On the one hand, the *Reports* state that the listing of a substance is not to be taken to indicate that it poses a risk to persons in their daily lives. On the other hand, labeling a substance as a "known" or "reasonably anticipated" carcinogen is almost certain to be understood to indicate that such substance either definitely will cause cancer to exposed persons, or is likely to. And the Introductions to the *Reports* themselves indicate that their purpose is to affect personal choices and reduce exposures, based on the assumption that any reduction in exposure will bring about a reduction in the incidence of cancer.

The level of exposure and consequently the dose to an individual of any substance are crucial in determining whether the effect on that individual will be beneficial, innocuous, or harmful. Yet such information is not communicated by the *Reports*.

We think it is time to question seriously whether Congress intended the *Reports* to be so confusing and lacking in useful information, or whether Congress needs to revisit the directions it gave to the Agency. If the *Reports* cannot provide more useful information to the public, perhaps they should be discontinued and the resources better invested in basic research into causes and treatments for disease.

We commend you and your staff for seeking public comment on these issues, and we trust that you will understand that we offer these views in a constructive spirit.

Respectfully,

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