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Regulatory and Trade
Counsellors

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Via FedX

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive, Bldg. 4401
Research Triangle Park, NC 27709

Comments for the re-review of
the 2,3,7,8-TCDD listing proposed for the
Report on Carcinogens, Ninth Edition

Dear Dr. Jameson:

The following comments are made in response to the Department of Health and Human Services *Federal Register* notice of April 15, 1998, which announced that there would be a re-review of this proposed listing and that there would be a public comment period until June 15, 1998. The notice stated that the NTP Director had determined "that the October 30 & 31 public review of TCDD may not have been adequate..."

We believe that there were many inadequacies in that review (as well as the RG1 and RG2 reviews), and we have previously commented on many of them; however, in these comments we focus mainly on one inadequacy that we believe is determinative: TCDD cannot be listed in the "known" category of the *Report on Carcinogens* ("RoC") because all of the human evidence deemed supportive is from studies of high occupational exposures to chemical mixtures in which dioxin was a contaminant, and the listing proposal is in terms of TCDD alone. There is no human evidence outside the scenario of high occupational exposure to mixtures that would support such a revised listing in the RoC. In addition, TCDD cannot be listed even as part of a mixture unless a significant number of persons in the United States are still exposed to such mixtures.

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1. **An RoC Category 1 listing ("known to be carcinogenic to humans") must be based solely on human evidence which is sufficient to indicate a causal relationship. The RoC criteria, as revised in 1996, do not allow for mechanism of action data, animal data, or any other type of data to compensate for insufficient human evidence.**

We have previously examined the revised criteria, and the records of deliberation leading up to their promulgation in September 1996, and have found that the record shows without any doubt that the above is true (1). During the October 1997 public meeting of the RC Subcommittee, the criteria were inaccurately described in this regard, and therefore there was much discussion during the deliberations on dioxin concerning mechanism of action data and the significance of the animal data. Such discussion was not relevant and should not be allowed to confuse the re-review (2).

2. **The IARC reclassification of TCDD to its Group 1 ("carcinogenic to humans") does not support the NTP proposal to list TCDD in its category 1, since IARC found that the human evidence was "limited" and not sufficient to infer a causal relationship.**

The IARC classification criteria were revised in 1991 to state explicitly that mechanistic data could, in exceptional circumstances, be used to compensate for human evidence that is less than sufficient. Such is not the case with the current RoC criteria. Nevertheless, the opening presentation to the RC Subcommittee by Dr. Arnold Schecter stated that "[t]he [RoC] nomination [by the prior review groups] took into account the IARC classification of TCDD as a Group 1 'Known Human Carcinogen' [sic] (IARC Monograph Vol. 69, 1997)." (3) And many of the RC Subcommittee members (probably abiding by Dr. Lucier's description of the criteria at the start of the meeting), clearly considered the weight of the mechanistic and animal data.

As noted by many of the academic experts who sent written comments to the RC Subcommittee, IARC found that the human evidence was "limited". Under the RoC criteria, such a finding precludes a category 1 listing. The RoC program has adopted similar weight-of-evidence guidance and has traditionally deferred to IARC findings on the weight of the human evidence.

One of the stated reasons for IARC finding that the human evidence was limited was the inability to rule out possible confounding (4). The RoC lead presenter, Dr. Schecter, however, did not discuss this aspect of the IARC evaluation, particularly in relation to the occupational cohort studies. Since the RoC criteria require classification in category 2 when "confounding factors could not adequately be excluded", the IARC evaluation for this reason could at most support RoC listing in category 2, and argues against listing in category 1.

3. **To the extent the human evidence might be considered indicative of carcinogenic hazard, it indicates only hazard due to occupational exposures to mixtures in which TCDD was a contaminant. All of the occupational cohorts relied on for the RoC listing proposal involved**

exposures to mixtures including phenoxy herbicides, chlorophenols, and dioxins. There is no way to isolate TCDD for evaluation and list it apart from those mixture exposures.

In his opening presentation, Dr. Schecter listed as one of the two arguments against listing TCDD as "known" that "[h]umans, including occupational cohorts exposed to dioxins, are also exposed to mixtures of other carcinogenic substances." While this argument was not stated with precision, since dioxin is actually included in the occupational mixtures, it should have been sufficient to alert the Subcommittee to a key issue. The lead reviewers for the Subcommittee also made this point. Unfortunately, this important point was subsequently touched upon only briefly in the subsequent Subcommittee discussions, and most discussion of potential confounding concerned smoking and asbestos rather than dioxin as a contaminant in occupational mixtures.

All of the human studies principally relied on for the RoC listing proposal are studies of occupational cohorts. All of those worker cohorts were extensively exposed to chemical mixtures that included phenoxy herbicides and chlorophenols (as well as other substances and derivatives) as well as TCDD, which was present as a contaminant. This basic point was often emphasized in the published study reports themselves and their titles, along with cautions regarding potential confounding. These points regarding the individual study reports are summarized below. These four cohorts, and the international cohort in which three of them were included (Kogevinas et al.), are isolated in Table 38 of the 1997 IARC Monograph (at 192).

Becher et al. (German cohort) (5)

- The title of the article is "Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins".
- The plants (Boehringer-Ingelheim and Bayer-Uerdinger) produced, and workers were exposed to --

Boehringer-Ingelheim

- 2,4,5-TCP
- 2,5-DCP
- 2,4,5-T acid
- 2,4,5-T esters

Bayer-Uerdinger

- 2,4,5-TCP
- possibly also alkylated anilines, acetanilide, ethanethol, and alkylated chloroformates
- The study report notes that IARC has classified phenoxy herbicides and chlorophenols in Group 2B ("possible human carcinogens").

- The study report states conclusions in terms of workers "exposed to phenoxy herbicides, chlorophenols, and dioxins".

Fingerhut et al. (cohort from 12 U.S. plants) (6)

- The plants were producing 2,4,5-TCP and derivatives contaminated with TCDD, including --
 - 2,4,5-T (trichlorophenoxyacetic acid)
 - Silvex (2-(2,4,5-trichlorophenoxy) propionic acid)
 - Erbon (2-(2,4,5-trichlorophenoxy) ethyl 2,2-dichloropropionate)
 - Ronnel (0,0-dimethyl 0-(2,4,5-trichlorophenol) phosphorothioate)
 - hexachlorophene (2,2'-methylene-bis[3,4,6-trichlorophenol])
- The authors stated that they could not conclude that there was a carcinogenic effect, one reason being that they could not assess TCDD alone; the workers were exposed concurrently to the chlorophenols and phenoxy herbicides, and possibly numerous other chemicals. (At 217, 212)
- The EPA Science Advisory Board's 1995 report also noted the possibility of confounding in this study due to exposures "to a wide variety of potentially carcinogenic agents in addition to dioxin." (2, at 51)

Hooiveld et al. (Dutch cohort) (7)

- The title of the study report does not even mention TCDD: It is in terms of a cohort "occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants".
- The study report's conclusions are in the same terms.
- The study report notes the 1987 IARC evaluations of chlorophenoxy herbicides, chlorophenols, and TCDD (discussed below).

Ott & Zober (German BASF accident cohort) (8)

- The exposures studied were accidental chemical releases from a TCP production unit, and associated cleanup.
- The study report noted that the risk estimates could be affected by confounding.

Kogevinas et al. (international cohort including three of the above cohorts) (9)

- The cohort included the mixture exposures noted above for the occupational cohorts.

- The title clearly reflects the nature of the mixture exposures: phenoxy herbicides and chlorophenols contaminated with TCDD.
- The findings indicated that "exposure to herbicides contaminated with TCDD and higher chlorinated dioxins may be associated with a small increase in overall cancer risk and in risk for specific cancers."

Some of this exposure information is also contained in Table 33 in the 1997 IARC Monograph on TCDD, although in some cases the Table does not reflect that exposure to TCDD was to TCDD contained in a mixture of phenoxy herbicides and/or chlorophenols.

It is interesting that the RoC Sept. 1997 Draft Background Document refers to the latest Seveso findings as supporting the listing proposal. Many of the outside academic commenters who wrote or spoke to the RC Subcommittee pointed out that the latest Bertazzi et al. findings were actually inconsistent with the conclusions drawn from the above industrial cohort studies. The Seveso studies have displayed a mix of findings different from the worker cohorts. This may be due to differences in the exposures, although, like the worker cohort studies, the exposures were to a mixture released from a plant producing chlorophenols. The 1989 Bertazzi et al. article stated that the chemical cloud that was released from the Medea TCP production plant in the accident was a "fluid mixture, containing mainly 2,4,5-trichlorophenol, sodium trichlorophenate, ethylene glycol, and sodium hydroxide", and that later TCDD was found (10). In their 1994 book chapter, Bertazzi & di Domenico characterized the release as a chemical cloud which "entrained nearly 2900 kg of organic matter, including at least 600 kg of sodium trichlorophenate and an amount of TCDD which is still being evaluated." (11) In the now-published 1997 article referenced as "in press" in the Sept. 1997 RoC Draft Background Document, Bertazzi et al. state that TCDD exposure "was relatively pure and substantial". (12) The variances in these exposure characterizations appear to indicate difficulty in actually ascertaining the true mixture, unlike the situation with regard to the occupational cohorts where it appears that the nature of the exposures could be ascertained with a higher degree of certainty due to their occurrence in a relatively confined area, and often under normal operating conditions. The 1997 article by Bertazzi et al. (12) states: "The exposure level and pattern of the Seveso population were different from that of cohorts in occupational settings [citing the 1997 IARC TCDD Monograph], where mixed exposures are common."

IARC has classified chlorophenols and chlorophenoxy herbicides in its Group 2B ("possibly carcinogenic") based on "limited" human evidence since 1986 (13). They were re-examined in 1987 (14). The evaluations of both noted that TCDD was included as an "impurity", and the 1986 findings were specifically in terms of "occupational exposure". These evaluations found that some subcohorts showed elevations of cancers of the following types --

- STS
- lung
- non-Hodgkins lymphoma
- nasal and nasal-pharyngeal

TCDD was not classified separately by IARC until 1987, when it was also put in Group 2B, based on "inadequate" human evidence and "sufficient" animal evidence. The TCDD report specifically noted the classifications for chlorophenols and chlorophenoxy herbicides and the occurrence of TCDD as an "impurity" in 2,4,5-TCP and 2,4,5-T. The 1987 TCDD evaluation noted elevations in cancers similar to those noted in association with chlorophenols and chlorophenoxy herbicides, with the exception of lung cancer. The IARC evaluation of the human evidence in 1997 changed from "inadequate" to "limited", based on the occupational cohorts discussed above, and with specific noted reservations regarding the inability to rule out confounding from other occupational exposures (as previously noted). This revised characterization of the human evidence brought the characterization for TCDD into line with the existing classifications for the chlorophenols and chlorophenoxy herbicides ("limited" human evidence), which cannot be separated from TCDD in the relevant studies. The inability to separate the effects of TCDD from the products in which it was found was specifically noted by IARC in its 1997 Monograph on TCDD and related compounds (e.g., at 137 and 336).

The RoC Program classified TCDD in category 2 in the *Seventh Annual Report on Carcinogens* (Summary volume at 369-72), based on "sufficient" evidence in animals and "no adequate data" in humans. In reporting on the human evidence, the 7th RoC noted that "[t]here are no reports of human exposure to TCDD alone", but that there were numerous studies associating cancer with exposure to "phenoxyacetic acids or chlorophenols, probably contaminated with TCDD", during "manufacture or use of 2,4,5-trichlorophenol and/or 2,4,5-trichlorophenoxy acids", and "herbicides contaminated with TCDD". The Report also noted that "production of 2,4,5-T and 2,4,5-trichlorophenol has been discontinued in the United States...."

The only chlorophenol classified by the RoC to date is 2,4,6-trichlorophenol, which was classified in category 2.

Finally, it should be noted that, although animal data cannot be used as evidence for RoC category 1, the nature of the experimental animal data highlights its lack of relevance for the human situation. The animal experiments have been conducted with pure TCDD, in contrast to the human occupational studies involving exposures to complex mixtures in which TCDD was an impurity.

In summary, the occupational cohort studies relied on in the Sept. 1997 RoC Draft Background Document for TCDD, the IARC evaluations for chlorophenols, chlorophenoxy herbicides, and TCDD, and the previous NTP evaluation of TCDD all recognize that the exposures to TCDD cannot be separated from the exposures to those other occupational chemicals which have been classified as potential carcinogens -- they occur as a mixture and the human evidence for all of them has been evaluated consistently as "limited" or "not adequate".

- 4. If the listing for TCDD is to be revised for the Ninth Edition of the RoC, it can be scientifically accurate and legitimate only if it reflects that the human evidence for increased cancer incidence is**

restricted to occupational exposures to mixtures of chlorophenols and/or chlorophenoxy herbicides in which TCDD occurs as an impurity. Even if the listing proposal were limited to occupational exposures to mixtures containing TCDD, however, the human evidence appears to be too weak to justify a category 1 listing, as indicated by the IARC evaluation of the human evidence. If such a listing were to be made, however, it would be contrary to the Congressional directives for the RoC Program unless it could be determined that there is a "significant number of persons residing in the United States" who are still occupationally exposed to such mixtures.

The 1996 revisions to the RoC criteria for category 1 to include "mixture" clarify that a listing could be made in conformance with the human evidence in this instance. However, such an occupational mixture listing can be made under the statute only if it can be determined that "a significant number of persons residing in the United States" are still exposed to such mixtures. 42 U.S.C. 241(b)(4)(A). If, as indicated by the TCDD entry in the 7th Edition of the RoC (at 371, 1994), such a determination cannot be made, TCDD cannot be listed even as part of an occupational exposure mixture. The discussion of human exposure in the September 1997 Draft Background Document is clearly inaccurate in this regard, particularly with its references to food as a primary source of exposure and to continued wide use of "Agent Orange".

Even if a determination of significant current U.S. occupational exposures can be made, there may be significant differences in the mixtures to which U.S. citizens are exposed and the exposures which were studied in other countries, such as Germany and The Netherlands. It is noteworthy in this connection that shortly after the RoC listing criteria revisions, a principal official in the RoC program, Dr. Lucier, noted that when occupational exposures are classified by the RoC program, there was "a consensus [among the RC Subcommittee] that qualifiers needed to be included with these references indicating that some of these processes, occupations and mixtures might not be applicable to current practices in the United States." (15)

* * *

Thank your for considering these comments.

Sincerely,


Jim J. Tozzi
Director

References and Notes

1. Multinational Business Services, Inc. ("MBS") wrote to the Director of the National Toxicology Program, Dr. Olden, on November 26, 1997, and provided specific documentation to support this position. That letter, which supplemented MBS written and oral comments before the RC Subcommittee, is incorporated by reference into these comments, along with our letter of January 31 requesting the issuance of guidance to staff and review committees clarifying this matter. The documentation cited in that letter, along with other records, shows conclusively that (a) the RoC listing criteria were not revised to allow consideration of other than human evidence in September 1996; and, in particular (b) references to consideration of mechanistic data and scientific judgment based on all types of data applied only to the category 2 criteria. The one change in the category one criteria which is pertinent to our comments here was insertion of the term "mixture" along with "substance" and "agent".
2. Even if mechanistic, animal, or other data could be used to add to the weight of the evidence, it is not relevant from a scientific perspective: (1) TCDD is a receptor-binding substance, and as such, biological outcomes are notoriously variable among species. See the report of the International Panel on Carcinogen Risk Assessment (Ames BN, Boyle P, Doull J, Galli CL, Greim H, Hayashi Y, Hill RN, Kimbrough RD, Krewski D, Kroes R, Monson RR, Munro IC, Rajewsky MF, Scheuplein RJ, Sugimura T, Swenberg JA, Travis CC, Whysner J, Williams G, Sieber SN), "The use of mechanistic data in the risk assessments of ten chemicals: An introduction to the chemical-specific reviews", *Pharmacol. Ther.* 71(1/2):3-5, at 4 (1996); and the chemical-specific review of 2,3,7,8-TCDD by Whysner J and William GM, "2,3,7,8-tetrachlorodibenzo-*p*-dioxin: Gene regulation, cytotoxicity, enhanced cell proliferation, and tumor promotion", *id.* at 193-223. This international panel was convened by the American Health Association under support by a grant from the U.S. National Cancer Institute. The panel oversaw the chemical-specific reviews, including the Whysner-Williams review of dioxin, which covered data at least through 1994. In its overview, the Panel stated: "Further research is required to determine whether the tumorigenic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in rodents apply to humans. [T]he mechanisms producing tumors in rodents may not be effectively operative in humans at any plausible exposure level." At 4. See also the Letter to the Editor of *Risk Analysis* by 20 scientists (mainly U.S. university professors in pharmacology and toxicology), "The dose-response model for dioxin", 18(1):1-2 (Feb. 1998). With regard to TCDD, the letter called attention to "the known, extensive interspecies variation in the biological outcomes of receptor-binding substances." Finally, see the U.S. EPA Science Advisory Board review of the draft EPA 1994 risk assessment for dioxin and related compounds, "An SAB Report: A Second Look at Dioxin" (Sept. 1995), at 49-51. (2) The non-human experimental data is based on exposure to pure dioxin, rather than exposure to a mixture that includes dioxin, as is the case with the human evidence being relied upon for the RoC listing proposal.

3. P. 1 of overheads used in presentation, and p. 3 of transcript. The reference to the IARC category as "known human carcinogen" is inaccurate. IARC does not use the term "known". This inaccuracy might have led the reviewers to assume that the IARC classification was identical, or at least very similar, to RoC category 1, when there are substantial differences between the two organizations' category definitions, as was clear from the IARC reclassification of TCDD to its Group 1 based on mechanistic data. As discussed herein and in previous MBS comments, RoC category 1 does not allow mechanistic data to be used to compensate for human evidence which is less than sufficient to infer a causal relationship.
4. Summary of the human data in Monograph 69 at 337. (There are references to potential confounding from other occupational chemicals with regard to lung cancer and also all cancers combined. In addition, it is noted that the data on STS also showed strong positive trends with estimated concurrent exposures to 2,4-D and 2,4,5-T.)
5. Becher H, Flesch-Janys D, Kauppinen T, Kogevinas M, Steindorf K, Manz A, and Wahrendorf J, 1996, "Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins", *Cancer Causes and Control* 7:312-21.
6. Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steenland K and Suruda AJ, 1991, "Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin", *New Eng. J. Med.* 324:212-18; and "Mortality among U.S. workers employed in the production of chemicals contaminated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)", 1991 (same authors, same study), U.S. Dept. of Health and Human Services, National Institute of Occupational Safety and Health, NTIS PB 91-125971.
7. Hooiveld M, Heederik D, Kogevinas M, Boffetta P, Needham LL, Patterson DG Jr., Bueno de Mesquita HB, 1998, "Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants", *Am. J. Epidemiol.* 147(9):891-901.
8. Ott MG & Zober A, 1996, "Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident", *Occup. Envir. Med.* 22:47-50.
9. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno de Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N & Saracci R, 1997, "Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols and dioxins: An expanded and updated international cohort study", *Am. J. Epidemiol.* 145:1061-75.
10. Bertazzi PA, Zocchetti C, Guercilena S, Consonni D, Tironi A, Landi MT, Pesatori AC, 1997, "Dioxin exposure and cancer risk: A 15-year mortality study after the 'Seveso Accident'", *Epidemiol.* 8(6):646-52.

11. Bertazzi PA & Zocchetti C, 1989, "Ten-year mortality study of the population involved in the Seveso incident in 1976", *Am. J. Epidemiol.* 129:1187-99.
12. Bertazzi PA & di Domenico A, 1994, "Chemical, environmental, and health aspects of the Seveso, Italy, accident", In: Schecter A, ed., *Dioxin and Health* 587-632 (Plenum Press).
13. IARC Monograph 41, 319-56, 357-406 (1986).
14. IARC Monograph Supplement 7, at 154-56, 156-60, 350-54 (updating Monograph Vols. 1-41) (1987).
15. "Summary Minutes" of NTP Board of Scientific Counselors meeting Dec. 13, 1996, at 3. The comments of the non-member NIOSH scientist at the October RC Subcommittee meeting -- that most NIOSH scientists would favor the new RoC listing proposal -- can be considered appropriate only if the individual had in mind the occupational situation which is within the purview of NIOSH. An RoC listing in category 2 could apparently be maintained for TCDD as an isolated substance based on sufficient animal carcinogenicity data under the current listing criteria. However, if retention of TCDD in category 2 is to be considered, in accordance with the revised RoC listing criteria, which provide for consideration of mechanism of action data and broad use of scientific judgment for category 2 listing decisions (but not for category 1), special attention should be paid to the extensive general evidence of inter-species variability in the case of receptor-binding substances (see note 2, above), including the lack of findings of liver cancer association in human studies. At the least, if a category 2 listing is maintained, these points should be noted in the RoC entry in commenting on the relevance of the animal data.