70278 Appendix L

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December 13, 1991

Dr. Erich W. Bretthauer
Assistant Administrator for Research and Development
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Dr. Bretthauer:

Attached are GE's written comments regarding EPA's Scientific Reassessment of Dioxin. These comments supplement oral comments made at the November 15 public meeting.

While GE is encouraged by EPA's efforts to develop a biological dose-response risk model for TCDD toxic effects, we are concerned about the concurrent plans to assess toxic equivalency factors (TEFs) for certain PCB congeners and include these data in estimates of risk for environmental mixtures. We recognize the attractiveness of this approach in principle, but we do not believe that currently available scientific data justify moving forward with this approach, especially in the context of the short-term, limited-scope dioxin reassessment program.

Specifically, our comments show that toxic equivalents calculated for PCB congeners are not additive (an assumption implicit in the TEF paradigm) and do not predict with a reasonable level of accuracy the toxicity of PCB mixtures in terms of AHH induction, immunotoxicity or carcinogenicity. Since the issue of additivity is not part of EPA's reassessment program, it appears that EPA might have relied too heavily on incomplete analyses presented at the 1990 PCB-TEF workshop.

We believe that this crucial failing of the TEF approach should convince EPA to disconnect the complex question of TEFs for PCBs from the dioxin reassessment and to establish a broader scope and longer time-frame study of the utility of PCB TEFs.

I would be happy to discuss this matter with you and/or EPA scientists at your convenience.

Steve Hamilton

SBH/cas
Attachment

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December 13, 1991

To: Erich W. Bretthauer
Assistant Administrator for Research and Development
U.S. Environmental Protection Agency

Re: GE's Comments on EPA's Scientific Reassessment of Dioxin Risks

Introduction

EPA's program to assess the emerging scientific information concerning the mechanism involved in the expression of toxic effects resulting from exposure to 2,3,7,8-TCDD (dioxin) is a promising and significant effort. It represents the first attempt to develop a biologically based dose-response model and incorporate it into risk assessment.[1] This attempt has received strong support from the scientific community and the public, as demonstrated at the November 15, 1991, public meeting.[2] These comments supplement oral comments made by S.B. Hamilton at that public meeting.

EPA has also incorporated into its dioxin reassessment the determination of toxic equivalency factors (TEFs) for various "coplanar" PCB congeners and their mono-ortho-chloro derivatives, based on the belief that these congeners express toxicity similarly to dioxin. EPA would measure levels of "coplanar" PCBs in human serum samples, for which dioxin/dibenzofuran values are already known, and subsequently determine where humans fit on the dose-response curve for enzyme induction. EPA would then assess the risk for all health effects related to exposure to dioxin and dioxin-like compounds.

This approach is fine in principle, since it attempts to combine several different chemical families into one formula for estimating risk, but it is one against which certain scientific information, which will be summarized below, argues strongly. GE recommends that this issue be studied separately from the dioxin risk reassessment, with a broader research agenda than that currently planned by EPA.

Discussion

In opening remarks at the December, 1990, Workshop on the Application of Toxic Equivalency Factors (TEFs) to PCBs[3], Dr. Donald Barnes presented "seven guiding criteria for the successful application of TEFs to any given complex mixture." One of the most important of these was "Demonstrated additivity between the toxicity of individual congeners." Dr. Barnes further stated that "The use of TEFs implicitly presumes additivity, so there should be some evidence that additivity is a reasonable assumption for the group of chemicals in question, in this case PCBs." Additivity is crucial and is easily tested based on available data.

Dr. Stephen Safe presented data at the same workshop that he regarded as "Limitations of the TEF approach for commercial PCB mixtures ..." Based on his calculation of toxic equivalents (TEs) using analytical data for coplanar congeners (IU PAC #s 77, 126 and 169) from Kannan (1988)[4], Safe calculated expected ED_{50} values of AHH induction and immunotoxicity for Aroclors 1242, 1248, 1254 and 1260 and compared them to observed values for those Aroclors. Based on these comparisons he concluded, regarding immunotoxicity, that "for Aroclors 1254 and 1260, the TEF approach provides good correspondence between the calculated values and the observed values. The situation is different for the lower chlorinated Aroclors..... For these two lower chlorinated Aroclors, therefore, the risk assessors would overestimate the toxicity." Similarly, in the case of AHH induction, he concluded that TEFs overestimated the toxicity of the lower chlorinated Aroclors, but provided reasonably good correspondence for Aroclors 1254 and 1260.

As indicated by Dr. Safe, his estimates of TEs included only contributions from the coplanar congeners The mono-ortho-coplanar congeners, which are now included in EPA's assessment of TEFs*, were not included. Contributions to TEs from these congeners can now be included based on analytical data from Schulz, et al. (1989)[5] for the eight mono-ortho congeners for which TEFs have been assigned. (Unfortunately, Schulz, et al., did not analyze Aroclor 1248, so further comparisons cannot be made regarding this Aroclor. However, Aroclor 1232 can be included since it is known to be a ~50-50 mixture of Aroclors 1221, which contains no TEs, and 1242. The TE value is assumed to be 50% that of Aroclor 1242.) The recalculated TEs for these Aroclors and Clophen A 30 are given in Table I.

* Dr. Safe agrees that it is appropriate to include data on mono-ortho-coplanar congeners in calculating TEs (personal discussion with S. Safe, December, 1991).

Table I

TCDD Equivalents in PCB Mixtures (ug/g)

Mixture	Coplanar Congener TEs[1]	Mono-ortho congener TEs[2]	TEs Total
Aroclor 1232[3]	27	13	40
Clophen A 30[4]	39	15	54
Aroclor 1242	54	26	80
Aroclor 1248	67	NA	NA
Aroclor 1254	11	129	140
Aroclor 1260	3	20	23

1 Coplanar congener data for Aroclors 1242, 1254 and 1260 are from Kannan (1988), and converted to TEFs by Safe (EPA - 1991).
2 Mono-ortho coplanar congener data are from Schulz (1989) and converted to TEs using a TEF of 0.001.
3 Aroclor 1232 is a 50/50 mixture of 1221, which contains no TEs, and 1242. Therefore TEs are assumed to be half that of 1242.
4 Clophen A 30 data are from Schulz (1989).
NA = Not available

Expected ED50 values for immunotoxicity and AHH induction were recalculated using the total TEs from Table I and the method of calculation described in EPA (1991). Results are given in Tables II and III, respectively, along with the original expected values (using only coplanar congener TEs) and test results observed for the Aroclors (EPA, 1991). Finally, ratios of observed to recalculated expected values are given. The results of this reanalysis indicate that TEFs overestimate toxicity in every case. In every case but one, the overestimation exceeds an order of magnitude. Therefore, it is clear that the principle of additivity is not met for two of the basic indicators of dioxin-like toxicity, AHH induction and immuno-

toxicity, and that toxic equivalents will substantially overestimate the toxicity of PCB mixtures.

Table II

Limitations of the TEF approach for Commercial PCB Mixtures
Immunotoxicity Studies in Mice

Mixture	Calculated ED_{50} (mg/Kg) Coplanar only*	Recalculated ED_{50} (mg/Kg) Coplanar and Mono-ortho	Observed ED_{50} (mg/Kg)*	Observed/ Recalculated ED_{50}s
Arocior 1232	-	19	464	24
Arocior 1242	14	10	391	39
Arocior 1248	11	NA	190	NA
Arocior 1254	70	6	118	20
Arocior 1260	257	33	104	3

* Source: Workshop Report on Toxicity Equivalency Factors for Polychlorinated Biphenyl Congeners, EPA/625/3-91/020, June 1991.

NA = Not available

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Table III

Limitations of the TEF approach for Commercial PCB Mixtures Based on AHH Induction in Rats

Mixture	Calculated ED_{50} (mg/Kg) Coplanar only*	Recalculated ED_{50} (mg/Kg) Coplanar and Mono-ortho	Observed ED_{50} (mg/Kg)*	Observed/ Recalculated ED_{50}s
Aroclor 1232	-	32	402	13
Aroclor 1242	23	16	450	28
Aroclor 1248	19	NA	282	NA
Aroclor 1254	116	9	440	49
Aroclor 1260	426	55	732	13

* Source: EPA/625/3-91-020, June, 1991

NA = Not available

An even more important test of the utility of toxic equivalents for the estimation of PCB risks is the issue of carcinogenicity, which is the basis for risk assessments for both dioxin and PCBs. The recent update of liver tumor pathology carried out by the Institute for Evaluating Health Risks (IEHR) provides valid data for comparing tumor potency of PCB mixtures with levels of TEs. Data in Table IV indicate that there is no correlation between the daily feedings of TCDD equivalents contained in the PCB mixtures Clophen A 30, Aroclor 1254 and Aroclor 1260 with the cancer potency resulting from long-term feeding studies in rats. Secondly the daily feedings of TCDD equivalents in the studies involving Clophen A 30 and Aroclor

1254 were 2.7 and 6.5 times, respectively, the daily feeding of TCDD in the Kociba experiment. If PCB toxic equivalents were behaving like dioxin and if the effects were additive, tests with these mixtures should have shown a powerful carcinogenic effect. Both of these tests were negative.

Summary and Recommendations

EPA's Scientific Reassessment of Dioxin includes a plan to determine TEFs for the "coplanar" PCBs (IUPAC #s 77, 126 and 169) using a repeated exposure paradigm to account for pharmacodynamic factors. This would seem to be a better approach to determining the toxicity of individual congeners relative to dioxin than previously done. However, EPA appears to assume, implicitly that TEs are additive and reasonably predictive of the toxicity of mixtures. Data presented above indicates that assumptions about additivity presented in EPA (1991) are inappropriate, and that the TEF approach does not reliably predict the toxicity of PCB mixtures in terms of AHH induction, immunotoxicity or carcinogenicity. In other words, PCB congeners having certain dioxin-like properties when tested individually do not behave like TCDD in PCB mixtures. In our opinion, these analyses should lead EPA to reconsider its assumption about additivity and to restructure its dioxin reassessment program. Specifically, we recommend that EPA separate the PCB congener studies from the dioxin reassessment and establish a broad program to evaluate PCB congener TEFs and the utility of these to predict the toxicity of mixtures. This would enable the dioxin reassessment activity to concentrate on the more limited issue of a biological dose-response paradigm for dioxin without burdening it with the more complex issue of PCB congener TEFs

For questions and further information about these comments, contact Dr. Stephen B. Hamilton, Manager of Environmental Science and Technology, General Electric Co., 3135 Easton Turnpike, Fairfield, CT 06431; Telephone 203-373-3316..

Table IV

Limitations of the TEF Approach for Commercial PCB Mixtures Based on Carcinogenicity Studies in Rats

	Kociba TCDD[1]	Clophen A 30[2]	Aroclor 1254[3]	Aroclor 1260		
				Sprague Dawley Females[4]	Sprague Dawley Males[4]	Sherman females[5]
Dose mg/Kg/day	0.0001	5.0	4.65	3.45	3.45	4.57
TCDD Eq. (ug/Kg/day)	0.1	0.27	0.65	0.08	0.08	1.1
Cancer Potency Factor[6]		0.2*	0.3*	5.7	0.4	1.9

* Negative Studies

1. Kociba, et al. (1978)
2. Schaeffer, et al. (1984)
3. National Cancer Institute (1978)
4. Norback and Weltman (1985)
5. Kimbrough, et al. (1975)
6. Source, IEHR (1991)

References

1. U.S. EPA, 1991, Office of Research and Development, *"Dioxin Reassessment and Research."*

2. Public Meeting on EPA's Scientific Reassessment of Dioxin, November 15, 1991. Announced in Federal Register 56 50903-4.

3. U.S. EPA, June 1991, *"Workshop Report on Toxicity Equivalency Factors for Polychlorinated Biphenyl Congeners,"* EPA/625/3-91/020.

4. Kannan, N. et al., 1988 *Arch. Environ. Health*, 43, 11.

5. Schulz, D.E., et al., (1989) *Env. Sci. Technol.*, 23, 852-859,

6. Institute for Evaluating Health Risks, July 1, 1991. *Reassessment of Liver Findings in Five PCB Studies in Rats*; Submitted to EPA by John A. Moore, President, IEHR.

7. Schaeffer, et al., (1984) *Toxicol. and Appl. Pharmacol.* 75,272-288.

8. National Cancer Institute, 1978, *"Bioassay of Aroclor 1254 for Possible Carcinogenicity,"* NCI Carcinogenesis Technical Report Series, Number 38.

9. Norback, D.H. and Weltman, R.H., 1985, *"Polychlorinated Biphenyl Induction of Hepatocellular Carcinoma in the Sprague Dawley Rat,"Env. Hlth. Perspect.* 60 97-105.

10. Kimbrough, R., et al., 1975, *JNCI*, 55.6, 1453-1459.

11. Kociba, et al., 1978, Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8- tetrachlorodibenzo-p-dioxin in rats. *Toxicol. Appl. Pharmacol. 46, 279-303.*

Appendix K

TEF DEVELOPMENT FOR WILDLIFE EFFECTS

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GLWQI TEFs for Wildlife

Congeners	TEF Values
A. PCDDs	
Mono-, Di-, TriCDDs	0
2,3,7,8-TCDD	1
1,2,3,7,8-PentaCDD	0.5
other PentaCCDs	0
2,3,7,8-HexaCDDs	0.1
other HexaCCDs	0
2,3,7,8-HeptaCDDs	0.01
other HeptaCDDs	0
OCDD	0.001
B. PCDFs	
Mono-, Di-, TriCFDs	0
2,3,7,8-TCDF	0.1
other TCDFs	0
2,3,4,7,8-PentaCDF	0.5
1,2,3,7,8-PentaCDF	0.05
other PentaCDFs	0
2,3,7,8-HexaCDFs	0.1
other HexaCDFs	0
2,3,7,8-HeptaCDFs	0.01
other HeptaCDFs	0
OCDF	0.001

GLWQI TEFs for Wildlife

Congeners	TEF Values
D. PCBs	
a) Coplanar	
3,3',4,4',5-PentaCB	0.1
3,3',4,4',5,5'-HexaCB	0.05
3,3',4,4'-TetraCB	0.01
b) Monoortho coplanar	
2,3,3',4,4'-PentaCB	0.001
2,3,4,4',5-PentaCB	0.001
2',3,4,4',5-PentaCB	0.001
2,3',4,4',5-PentaCB	0.001
2,3,3',4,4',5-HexaCB	0.001
2,3,3',4,4',5'-HexaCB	0.001
2,3',4,4',5,5'-HexaCB	0.001
2,3,3',4,4',5,5'-HeptaCB	0.001

TEF OPTIONS FOR WILDLIFE RISK ASSESSMENTS

1. Use the current Agency endorsed TEFs for dioxins and furans, as proposed in the GLWQI.

   * Uncertainties with interspecies and endpoint extrapolations.

2. Use the PCB TEFs proposed in the GLWQI.

   * Uncertainties with interspecies and endpoint extrapolations.

   * Risk Assessment Forum workshop (U.S. EPA, 1991) did not endorse TEFs for human health, but did for wildlife.

     The logical basis and specific data sets for this conclusion not provided and specific TEFs not endorsed.

   * Given a 2 to 3 order magnitude range for some TEFs, which specific values are scientifically defensible?

3. Use the PCB TEFs but update as new research becomes available.

   * Given a 2 to 3 order magnitude range for some TEFs, which specific values are scientifically defensible?

   * In the context of the GLWQI, would a Tier 2 approach be appropriate?

   * No specific research for wildlife-based TEFs at this time.

4. Do not use TEFs until additional research completed.

   * Use appropriately conservative chemical-specific criteria.

   * No specific research for wildlife-based TEFs at this time.

TEF OPTIONS FOR WILDLIFE RISK ASSESSMENTS

SELECTION OF TEFs

	Birnbaum et al.[a]	Safe (1990)
A. PCDDs		
2,3,7,8-TCDD	1	1
1,2,3,7,8-PentaCDD	0.5	0.5
B. PCDFs		
2.3,7,8-TCDF	0.05	0.1
1,2,3,7,8-PentaCDF	0.001	0.1[b]
OCDF	0.001	0.001
D. PCBs		
(a) Coplanar		
3,3',4,4',5-PentaCB	0.01	0.1
3,3',4,4',5,5'-HexaCB	0.001	0.05
3,3',4,4'-TetraCB	10^{-6}	0.01
(b) Monoortho coplanar		
2,3,3',4,4'-PentaCB	10^{-5}	0.001
2,3,3',4,4',5-HexaCB	10^{-5}	0.001
2,3,3',4,4',5'-HexaCB	10^{-4}	0.001

[a]Unpublished data from Birnbaum et al. (US EPA, Health Effects Research Laboratory). TEFs based on hepatic EROD activity in rats orally-exposed to the above compounds after 30 days of a 90-day study. PCBs did not effect hepatic EROD activity and these TEFs are maximum values based on detection limits for the assay. Data at 90 days is not complete, but compared to 30-day data indicate that hepatic EROD activity in rats exposed to these dioxin, furan, and PCB congeners is decreased relative to activity in rats exposed to 2,3,7,8-TCDD.

[b]The TEF recommended by the NATO workgroup is 0.05.

Jackie Moya is directing an EAG study which reviews and re-evaluates the raw data for several creel surveys in different areas of the U.S. and Canada. The results of the re-analysis of these data will be available in several months. At that time we will forward them to you and can advise you on how they might affect the Phase II study. In the interim, it is our best professional judgement that the consumption rate of 30 grams/days (which is approximately 1 meal of 1/2 15 serving per week)is a reasonable assumption and is not overly-conservative. In fact, as noted above, it is significantly less than the intake factor of 54 grams/day listed in Superfund guidance (OSWER Directive 9285.6-03).

It should also be recognized that the Phase I study might have significantly underestimated consumption levels to highly exposed subpopulations. The Phase I study did not evaluate possible risks to subsistence fishermen, who by some estimates may consume fish at rates from 100-300 grams per day. The Phase II study should evaluate whether such a highly exposed subpopulation might exist in vicinity of the Hudson River.

When inquiring to several EPA Headquarters scientists, I was told that the ChemRisk survey of Maine anglers had been reviewed by several noted researchers on fish consumption studies, who concluded that the ChemRisk study is seriously flawed and should not be relied upon to estimate fish consumption rates for frequent fisherman. Their conclusions are shown below and their complete comments are enclosed for your review.

In his evaluation of the ChemRisk study for the Maine Department of Environmental Protection, Dr. Patrick C. West, Associate Professor of Natural Resource/Environmental Sociology at University of Michigan, severely criticized the study. In his summary he stated:

> "The ChemRisk study has systematically used methodological procedures and assumptions most of which in my judgement tend to bias the study towards low grams/person/day estimates for standard setting. It may not have been their intent to do so, but in my best judgement this was the result. These factors combined help explain why this study's low results are so far below almost all other credible fish consumption studies. In my opinion the ChemRisk study should not be used as a basis for setting standards for Dioxin in Maine but that is a determination the Maine DEP must make."

The ChemRisk study was also reviewed by Dr. Barbara A. Knuth, Assistant Professor of Natural Resource Policy and Management at Cornell University, who was retained as consultant for the Natural Resources Council of Maine. Dr. Knuth's evaluation was also highly critical of the ChemRisk study. She summarized her comments stating:

"The major flaws of recall bias and household-level fish consumption prevent accurate individual consumption rates from being devised from this data. The incomplete representation of this entire population of potential Maine freshwater fish consumers prevents accurate assessment of fish consumption suppression. The detailed review discusses these flaws in more detail and includes a discussion of less serious flaws that warn against using these data for any but the most general purposes. I believe the flaws in this study are severe enough to produce major underestimates of potential and actual fish consumption rates for Maine residents."

Effects of Cooking on PCB Levels

GE stated that it is reasonable to conclude that at least 25% of the PCBs found in the fish fillet will be lost as a result of cooking. During their presentation in New York, ChemRisk presented the results from studies that only showed decreases in PCB concentrations. In response to questions by EPA, they stated that they were not aware of any studies that showed increases in PCB levels. (We have since provided ChemRisk with references for studies showing increases in PCB levels.)

We disagree with this conclusion since our review of the scientific literature has identified several studies which reported an actual increase in PCB levels: Zabik et al. 1982 reported a 36% increase for deep fried carp, a 33% increase for charbroiled carp, and 13% increase for poached carp; Smith et al. 1973 reported at 1.3% increase for poached chinook salmon; Trotter et al. 1989 reported an 8% increase in PCB levels for baked bluefish.

These and other studies about the effects of cooking show considerable variation in results (both increases and decreases) depending upon species, cooking method, and portions of fish sampled. Therefore, we support the Region's position in the Phase I report of not assuming either an increase or decrease of PCB concentrations.

Compounding of Conservative Assumptions

In the meeting with GE on February 4, 1992, GE complained about the "creeping conservatism" of the Phase I risk assessment and the cumulative effects of compounding too many worst-case assumptions.

We agree with GE that it is important and necessary to evaluate the protectiveness or conservatism of the exposure scenarios as a whole not just on an individual basis. We disagree, however, with their contention that the combination of assumptions used in the exposure assessment of the Phase I study amount to an unrealistic worst case scenario resulting from the compounding of too many individual worst case assumptions. As we stated earlier, several of the assumptions were made using factors that are less conservative than those often used in Superfund risk assessments.

Monte Carlo Simulations

In the February 4, 1992, meeting GE proposed using a Monte Carlo simulation to estimate a distribution of PCB intake through fish consumption. The details of this proposal were not clear, and GE agreed to provide additional information for EPA comment.

Region II personnel stated that their risk managers will continue to use the Reasonable Maximum Exposure (RME) estimate as a basis for risk-based decisions until such time as the Agency's policy is changed. However, the Region was receptive to including a Monte Carlo simulation in the Phase II assessment as a type of sensitivity analysis.

EPA pointed out at the meeting that a Monte Carlo simulation is only as good as the input data. If some of the data are poor, the Monte Carlo simulation may obscure the degree of uncertainty in the exposure/dose estimates.

We in EAG believe that a properly constructed Monte Carlo simulation may provide dose estimates that are in some cases higher than the Phase I dose estimates. As pointed out above, the Phase I dose estimates are not, strictly speaking, RMEs since they are based on mean rather than 95th percentile average fish consumption values. Depending on how sensitive the Monte Carlo simulation is to the fish consumption values, a high end dose value (say a 95th percentile value) from a Monte Carlo simulation may well be greater than the Phase I dose estimate based on average consumption of 30 grams/day.

Conclusion

In conclusion, after reviewing GE's comments, the reviewers still believe that the Region's Phase I risk assessment is consistent with EPA's risk assessment guidelines and guidance. We would be glad to provide additional assistance during Phase II. If you have any questions, please call me at FTS 260-2588.

cc: Marina Stefanidis, Region II
Dave Bennett, OS-230
Michael Callahan, RD-689
Steve Ells, OS-510
Paul Simmon, Region II - ORC
Dorothy Canter, OS-110
Jim Cogliano, RD-689

Attachments