EPA's Scientific Reassessment of Dioxin
November 15, 1991
EPA Education Center Auditorium

Office of Research and Development
United States Environmental Protection Agency

8:30am-8:50am	Opening Remarks	*F. Henry Habicht II, Deputy Administrator, EPA*
8:50am-9:00am	EPA's Scientific Reassessment of Dioxin	*Dr. Erich Bretthauer, Assistant Administrator, Office of Research and Development*
9:00am-9:05am	EPA Panel Convenes	
9:05am-9:15am	Introduction of EPA Panel	*Dr. Peter Preuss, Director, Office of Technology Transfer and Regulatory Support*
9:15am-9:30am	Dioxin Toxicity: State of the Science	*Dr. Linda Birnbaum, Health Effects Research Laboratory, RTP, NC*
9:30am-9:50am	Components of the Dioxin Reassessment Process	*Dr. William Farland, Director, Office of Health and Environmental Assessment*
9:50am-10:05am	Health-Directed Research	*Dr. Linda Birnbaum, Health Effects Research Laboratory, RTP, NC*
10:05am-10:25am	Characterization of Toxicity and Risk of Dioxin in Aquatic Environments	*Dr. Philip Cook, Environmental Research Laboratory, Duluth, MN*
10:25am-10:45am	Question and Answer Session	
10:45am-11:00am	Break	
11:00am-12:10pm	Oral Comment	
12:10pm-12:50pm	Lunch	
12:50pm-3:45pm	Oral Comment	
3:45pm-4:00pm	Closing Remarks by EPA	

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Oral Comment Schedule

11:20am	William Sherman, S.D. Warren Company Research Laboratory
11:30am	Dr. Ronald O. Kagel, Chlorine Institute
11:40am	Dawn G. Goodman, PATCO Inc.
11:50am	Dr. Richard Clapp, ISI Center for Environmental Health Studies
12:00pm	Dr. Robert G. Kaley, II, Monsanto Company
	Lunch
12:50pm	William Greenlee, Purdue University
1:00pm	Kathy Gill, Northwest Paper and Pulp Association
1:10pm	Dr. Seymour Friess, Drill, Friess, Hays, Loomis and Schaffer, Inc.
1:20pm	Dr. John Whysner, American Health Foundation
1:30pm	Dr. Jim Hendrik, Mississippi State Medical Association
1:40pm	Peter de Fur, Environmental Defense Fund
1:50pm	Dr. Erik Rifkin, Rifkin and Associates
2:00pm	Joseph H. Guth, Natural Resources Defense Council
2:10pm	Dianne Cameron, Natural Resources Defense Council
2:20pm	John Tarrel, SODA Health and Environment
2:30pm	Stephen B. Hamilton, General Electric
2:40pm	Robert W. Morgan, M.D., Environmental Health Strategies
2:50pm	Dr. Melvin Andersen, Chemical Industry Institute of Toxicology
	Break
3:20pm	Dr. Barry Commoner, Center for the Biology of Natural Systems
3:30pm	Dr. Tom Webster, Center for the Biology of Natural Systems
3:40pm	Peter Montague, Greenpeace USA

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CHEMICAL
MANUFACTURERS
ASSOCIATION

ORAL TESTIMONY ON THE SCIENTIFIC REASSESSMENT OF DIOXIN

submitted to
U.S. ENVIRONMENTAL PROTECTION AGENCY

by
DR. ROBERT KALEY
on behalf of
DIBENZOFURANS/DIOXIN PANEL
CHEMICAL MANUFACTURERS ASSOCIATION

November 15, 1991

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My name is Dr. Robert Kaley, and I am Chairman of the Chemical Manufacturers Association Chemstar Panel on Chlorinated Dibenzofurans and Dibenzo-p-dioxins. The Panel commends the EPA on its initiative to consider recent developments in the science of the dibenzofurans and dibenzodioxins in an effort to bring the regulatory status of these chemicals more in line with the scientific status. We also appreciate the opportunity to present oral and written comment to the EPA as part of that process. We have previously written to Mr. Henry Habicht expressing our concerns in the matter to be addressed here and submit that letter and a transcript of these comments for your consideration.

Our remarks will address one issue in the reassessment program as outlined in the recent announcement from EPA. That issue involves the recent interest within the EPA in the development and promotion of Toxicity Equivalency Factors (TEFs) for certain polychlorinated biphenyl (PCB) congeners, most specifically the three or four so-called coplanar PCBs and eight structurally associated 'mono-ortho' congeners. These twelve are those being labeled by the recently coined term 'dioxin-like', which emphasizes as clearly as anything the source of our concern.

The current regulatory reassessment program includes two specific facets targeted at TEFs for PCBs. The CMA Panel urges caution and reserve in any attempts that the EPA might make to incorporate PCBs or other compounds in the current dioxin reassessment. It is our position that such incorporation within the time-frame established for the dioxin reassessment is scientifically premature, and in fact, such activity seems to run counter to the overall thrust of the reassessment, which is to use the best available scientific information.

A December 1990 workshop on TEFs for PCBs, organized by the EPA Risk Assessment Forum, suggested that the concept of TEFs for PCBs is premature and probably not based on firmly established science. However, there is clearly a strong movement within the Agency to adopt

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and use TEFs for the so-called dioxin-like PCBs. Indeed, based on primarily in vitro studies in a single research laboratory, numerical values for TEFs have been proposed for several groups of PCB congeners. Although these proposed values may very well reflect the receptor-binding potential of certain PCB congeners, it must be recognized that binding potential does not necessarily equate with any corresponding physiological endpoint.

It seems clear that the proposed TEFs do not represent realistic assessments of the potential of PCBs in general or even specific classes of PCBs to affect toxicological endpoints. The most telling example of inconsistency is carcinogenicity -- the endpoint on which dioxin risk assessment is based.

At the EPA workshop and in the recently published proceedings of that the workshop, data were presented indicating that the levels of Toxic Equivalents (TEQs) based on the proposed TEFs decrease with increasing levels of chlorination in commercial PCB products. In other words, TEQ calculations for 42% chlorinated PCB mixtures are much higher than those calculated for 60% chlorinated mixtures. However, the results generated in rodent chronic exposure studies are in the opposite direction with regard to the carcinogenicity. Only 60% chlorinated PCB mixtures have been demonstrated to give positive results in rodent carcinogenicity tests. This result has been recently confirmed in a reevaluation of the pathology slides from most of the PCB chronic exposure studies.

It does not seem appropriate to integrate TEFs for PCBs into a reassessment of dioxin toxicity when the most basic measure of risk for risk assessment, the cancer potency, is not consistent with calculated TEQs for PCB mixtures.

The value of the TEQ concept for PCBs mixtures with regard to other endpoints is no clearer, and in fact, similar contradictory results are evident for other endpoints. Another example is the information regarding immunotoxicity studies in mice. Again, the trend in TEQs in

the PCBs is in the opposite direction to the observed effect in the animal studies of PCB mixtures. As presented at the EPA TEF workshop, although the 42% chlorinated PCB mixture has nearly 20 times the TEQs of the 60% chlorinated mixture, the 60% PCB mixture is nearly 4 times as potent in the actual test.

With regard to the actual plans for the dioxin reassessment program, it is unclear from the announcements exactly what the EPA Health Effects Research Laboratory (HERL) program for TEFs for PCBs is to incorporate. It is certainly unlikely that any results will be generated that can outweigh the contradictory data generated in chronic exposure studies. Indeed, data generated in the same laboratory, which is now promoting TEFs for PCBs, indicates that with regard to certain endpoints, PCBs may act as antagonists to the effects of TCDD. It is not clear that this type of data is to be, or even can be, incorporated into a TEF scheme for PCBs. One of the criteria for the use of a TEF scheme is additivity of effects. Presumably, demonstrable antagonists would have to be treated by subtracting corresponding TEQs.

A second facet of the PCB-TEF component of the reassessment involves measurement of PCB congeners in blood samples for which PCDD and PCDF levels are already known. The plan states that HERL will then use these data to calculate TEQs in the general population. It is unclear what this exercise, which is likely to be very expensive, is to contribute to the dioxin reassessment process.

There is no question that HERL or its contractors will be able to generate values for the concentration of PCB congeners in blood samples, including congeners for which TEFs have been proposed. Further, given PCB congener concentrations and proposed TEFs, TEQs can be generated. However, it seems inappropriate to use non-validated TEFs which are based on <u>in vitro</u> studies, to generate TEQ values for the general population. This exercise is clearly 'putting the cart before the horse.'

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The more important question is what relevance these TEQs might have, even if they are generated. In the first place, the blood level data cannot be used to generate TEFs or validate proposed TEFs because there is no human health effect for which either a dioxin or PCB dose response curve is known; that is, there is no frame of reference on which to base TEFs. Secondly, the blood levels for PCB congeners should not be used to either add to or subtract from PCDD and PCDF TEQs in the general population because the results would not be meaningful. The reasoning is the same. There is no health effect in the general population that can be attributed to either PCBs or the dioxins and furans. Thus, any data generated by the HERL will be merely numbers in a scientific vacuum.

Another Panel concern is the potential use and/or misuse of the TEFs. The TEFs for PCDDs and PCDFs were recommended as interim procedures by the EPA after Science Advisory Board (SAB) review. An integral part of the SAB recommendation was an emphasis on the interim nature of the TEFs, a point specifically noted by Dr. Don Barnes in his opening remarks at the TEF workshop. However, Barnes also recognized that some persons were losing sight of the interim nature of the TEF procedure. Barnes issued a call to move beyond TEFs and develop a replacement procedure, based on good science. We concur in that call. And in light of that call, we question the establishment of TEFs for PCBs as part of a dioxin reassessment program. The incorporation of further interim factors at this time seems unlikely to increase our understanding of dioxin toxicology or to facilitate the risk assessment or risk management process.

We are also concerned about the potential misuse of TEFs in the regulatory process, whether the TEFs are for PCDDs and PCDFs or for PCBs. CMA member companies are aware of situations in which TEQ calculations are being used by state regulatory agencies for discharge limits in permits and for other enforceable actions. The EPA Risk Assessment Forum states clearly that its TEF recommendation was an interim procedure to facilitate risk assessment. Unfortunately, the

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Forum is unable to control the ultimate uses of the TEFs once they are issued.

We are therefore concerned that the addition of yet another layer of TEFs will contribute to still higher potential for inappropriate use in state or even federal regulatory programs. This concern is accentuated by our observation that the proposed TEFs for PCBs are not consistent with the known toxicology of PCBs.

In conclusion, we ask that the Agency groups responsible for the various facets of the dioxin toxicity reassessment program disassociate the premature and scientifically unsound proposals for TEFs for PCBs from the dioxin reassessment. If TEFs for PCBs are to be considered at all, that consideration should be a well thought out program in its own right, not as a tag-along to the timely and important dioxin reassessment.

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CHEMICAL MANUFACTURERS ASSOCIATION

Gordon D. Strickland
Vice President-Technical Services

August 1, 1991

Mr. Henry Habicht
Deputy Administrator
U.S. Environmental Protection Agency
West Tower, Room 1215
401 M Street, S.W.
Washington, D.C. 20460

Re: Dioxin and PCB Toxicity Equivalency Factors

Dear Mr. Habicht:

On June 28, 1991, representatives of the Chemical Manufacturers Association Dibenzofurans and Dibenzodioxins Panel met with Dr. Donald Barnes of the Science Advisory Board (SAB) to discuss Toxicity Equivalency Factors (TEFs) for dioxins and the development of TEFs for PCBs. Dr. Barnes suggested that a letter elaborating the Panel's concerns be sent to you. The Panel has subsequently reviewed its concerns with the CMA Polychlorinated Biphenyls Panel and this letter outlines the shared concerns of the CMA Panels.

The Panels have concerns in two particular areas:

1. Regulations relying on TEFs for PCDDs and PCDFs are being promulgated without sufficient appreciation of the complexities of such a scheme and without guidance as to how to deal with those complexities.

2. The current movement within the Agency toward the development of interim TEFs for certain PCB congeners is premature and not based on sufficient scientific information.

Both concerns are discussed in greater detail in an attachment to this letter.

The Panels encourage the Agency, through the SAB, Risk Assessment Council, and the Office of Research and Development, to provide ample opportunity for both internal and external review of both the development and the application of TEF schemes for PCDDs and PCDFs. We further urge EPA to consider carefully all implications of introducing TEFs for PCBs into risk assessment or regulatory schemes. As the cancer data exemplify, PCBs are <u>not</u> dioxins. Attempts to make them so by Agency science policy should be undertaken only if and when sufficient scientific bases exist.

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Specifically, we urge EPA to:

(1) Prepare for SAB and interested party review, guidance on regulatory application of the existing TEF scheme for PCDDs and PCDFs;

(2) Proceed slowly, with full opportunity for public and scientific review, with any work on PCBs; and

(3) Reflect the need for scientific caution in future EPA pronouncements, including presentations at the September 26, 1991 Dioxin '91 conference at Research Triangle Park.

The Panels would welcome the opportunity to cooperate with Agency scientists to follow through on these introductory discussions. Please contact Elizabeth Festa Gormley (202/887-1194), Manager of both Panels, if you wish further details of our concerns.

Sincerely,

Gordon D. Strickland

Gordon D. Strickland
Vice President
Technical Services

cc: Donald Barnes
Tony Baney
William Farland

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CONCERNS OF THE
DIBENZOFURANS AND DIBENZODIOXINS PANEL
AND THE
POLYCHLORINATED BIPHENYLS PANEL
RELATIVE TO
TOXICITY EQUIVALENCY FACTORS

The Chemical Manufacturers Association Panels for Dibenzofurans/Dibenzodioxins and Polychlorinated Biphenyls have reviewed their concerns on the use of toxicity equivalency factors (TEFs) with Dr. Donald Barnes of the Science Advisory Board (SAB). The Panels are concerned that regulations are being promulgated based on TEFs for polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). These regulations reflect a lack of appreciation of the complexities of using the TEF scheme. Second, the Panels are concerned about the development on interim TEFs for certain polychlorinated biphenyl (PCB) congeners which ultimately may be missused in a similar manner. Development of TEFs is premature and not based upon sufficient scientific data.

TEFs FOR PCDDs and PCDFs ARE BEING INCONSISTENTLY INCORPORATED INTO REGULATORY SCHEMES.

The EPA publication "Interim Procedures for Estimating Risks Associated with Exposures of Mixtures of Chlorinated Dibenzo-p-dioxins and Dibenzofurans (CDDs and CDFs) and 1989 Update", EPA/625/3-89/016, provides useful guidelines and precautionary language concerning this particular "...interim science policy." Recent experiences with TEFs for PCDDs and PCDFs provides useful information regarding the potential for inconsistent use and abuse of this admittedly interim procedure. It is unclear from the booklet, whether the Science Advisory Board (SAB) while accepting TEFs on an interim basis for the estimation of "health risks associated with exposure to mixtures of PCDDs and PCDFs for risk

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management purposes," intended to suggest that the scheme was also acceptable as a component of regulatory enforcement. Had this been the intent, the SAB, or EPA, should have provided more specific guidance on appropriate application of TEFs in the regulatory arena. TEFs were developed by the Science Advisory Board (SAB) and the Risk Assessment Council. Therefore, these bodies should provide the first line of responsibility and review.

Several recent examples illustrate the inconsistent application of TEFs to actual regulatory standards. The Texas Water Quality Commission has adopted a "Texas I-TEF" scheme for water quality standards, proposing 0.7 ppq TEC (Toxic Equivalent Concentration) for estuarine waters and 1.0 ppq TEC for fresh water. These standards would apparently be enforced even if no 2, 3, 7, 8-TCDD were present. In Connecticut, a standard of 1 pg/m^3 2,3,7,8-TCDD equivalents has been adopted for ambient air quality. And, as you are no doubt aware, in May the U.S. EPA proposed a rule regulating the disposal of sludge from pulp and paper mills which incorporates the TEF concept, albeit limited to 2,3,7,8-TCDD and 2,3,7,8-TCDF.

Each of the above proposals or regulations incorporates TEFs to calculate toxicity equivalents (TEQs or TECs). However, even among these examples there is inconsistency and problems in application of the TEF concept. The Texas I-TEFs do not include the hepta- or octachlorinated congeners, while the EPA rule only calculates TEQs based on the 2,3,7,8-substituted tetrachlorinated species.

Both regulators and the regulated community must be concerned about the proliferation of inconsistent TEF concepts. If TEFs are to be used at all for regulatory purposes the U.S. EPA must ensure that each application is clear and consistent.

There are two major problems with the use of TEFs in regulations. These problems, the inclusion of "not detected" (ND) values in TEC calculations, and the assumption of equal bioconcentrations of all congeners, need to be resolved before TEFs can be used in the

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regulatory arena. In many, if not most, cases, the analytical results for PCDD and PCDF congeners would be below detection limits for the particular analytical technique. Neither the EPA nor the SAB provide guidance on how to deal with values below the detection limit. How is the regulated community to incorporate "Not Detected" or "Not Quantifiable" values into the TEQ concept? Should one use zero or the detection or quantification limit as the concentration factor for all non-detected or non-quantifiable congeners? Statisticians prefer a value of one-half of the detection limit. Depending on the value chosen for "not detected", the calculated TEQ can vary by an order of magnitude. For a complex sample where all the congeners are below the detection limit, it is possible for the calculated TEQ to exceed the allowable level, even if no PCDDs or PCDFs are detected, depending on how "non-detects" are treated.

As Dr. Barnes acknowledged at the December 1990 EPA conference on TEFs for PCBs, TEFs are anything but 'interim.' For better or for worse, it seems that TEFs for PCDDs and PCDFs are likely to be used increasingly for regulatory purposes. Accordingly, it is critical that the US EPA accept the responsibility for providing guidance for their regulatory application. The SAB has endorsed the TEF concept for risk management; it has highlighted its advantage; and it has discussed the limitations and needs for further research. It must now advise the Agency how to implement TEFs in the regulatory arena in a manner that is scientifically defensible, environmentally meaningful, and economically viable.

THE CURRENT AGENCY PROPOSAL TO DEVELOP TEFS FOR COPLANAR PCBS IS PREMATURE.

We are also concerned about the development of TEFs for certain PCB congeners. As the concept of using TEFs for PCBs appears to be gaining momentum within the Agency, we urge caution as this approach is considered. Objective review of the conceptual basis of TEFs for PCBs reveals serious deficiencies. It is not clear that the TEFs for PCBs

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that are currently receiving the most attention are, in fact, at all representative of environmental and health endpoints of importance.

In December 1990 the U.S. EPA sponsored a workshop in Washington, D.C. to discuss the concept of Toxicity Equivalency Factors for PCBs. Dr. Barnes, et al., have prepared a summary of the workshop, and the proceedings are to be published by the conference organizers, presumably within the next several months (publication was originally anticipated for April). The currently proposed scheme would assign TEFs for three so-called 'coplanar' PCBs (TEFs range from 0.1 to 0.05) and a much lower default TEF (0.001) for 8 congeners with a single chlorine in an ortho position. (Barnes, et al., further suggest 0.00002 as a TEF for di-ortho congeners.) These proposed TEFs are primarily, if not exclusively, based only on in vitro studies done by Dr. Stephen Safe at Texas A & M. Arguments based on structure-activity relationships (SAR) have also played a large part in the development of the concept.

The TEF proposal has even reached the stage within the Agency that a novel acronym has been coined, "DL PCBs", for Dioxin-Like PCBs. This unfortunate phraseology reflects an attitude within the Agency that is not supported by the available scientific information. Indeed, even the most ardent supporters of the proposal acknowledge that many endpoints purportedly associated with in vivo toxicities of PCBs cannot be associated with "dioxin-like" activity. Few, if any, of the individual PCB congeners for which TEFs have been proposed have been tested in any in vivo system.

One fears that the PCB TEF system will not stand up to careful scrutiny. While the system may be appropriate to guide research and possibly even to assist risk managers conceptualize potential risks, it certainly is not strongly enough based to support regulatory standards.

A single example may provide the most telling argument for caution. Risk assessment and regulation of 2,3,7,8-TCDD, and by analogy the other PCDDs and PCDFs, is based almost exclusively on the cancer risk

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associated with these chemicals. Even though a wide range of animal toxicities are acknowledged to be associated with exposure to 2,3,7,8-TCDD and seem to result from the same receptor-mediated mechanism, it is the cancer endpoint that drives risk assessments and, thus, regulations. One of the primary driving forces for the development of TEFs for PCDDs and PCDFs was the lack of carcinogenicity data for the individual congeners. TEFs were, thus, largely developed so the cancer potency factor for 2,3,7,8-TCDD could be applied to PCDD and PCDF mixtures in clean-up situations.

Logic would argue that if PCBs, or more specifically selected PCBs, are to be managed or regulated based on TEFs and their 'dioxin-like' properties, those TEFs should bear some relationship to the endpoint of most concern within the Agency, cancer risk. Yet, the available animal data for PCBs provides evidence directly controverting this logic. Data presented by Dr. Safe at the December Washington conference indicate that the TEQs for commercial PCB products are highest in the lower chlorinated products such as Aroclor 1232 and Aroclor 1242. Aroclor 1260, the most highly chlorinated of the products discussed, has the lowest TEQ, as calculated by the proposed scheme. However, PCB products chlorinated at the 60% level or higher are the only mixtures for which there is sufficient evidence of rodent carcinogenicity. Dr. Safe acknowledged at the conference that the carcinogenicity of PCB mixtures has nothing to do with the 'dioxin-like' congeners. It is, therefore, inappropriate to treat these congeners as "dioxins" for risk assessment and regulatory purposes.

Barnes, et al., in Conclusion and Recommendation 2, p. 17, of their (to date not officially published) summary, state:

> The resulting DL TEQs should be added to the TEQs for CDDs and CDFs to estimate the total "dioxin"-like risk.

Given that the 'dioxin'-like risk is based on the cancer potency factor of 2,3,7,8-TCDD, it is scientifically improper to treat PCBs, or even coplanar PCBs, as if they were dioxins.

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This issue is exacerbated by the recent review of slides from PCB bioassays by the Institute for Evaluating Health Risks (IEHR). As you know from correspondence from John Moore, this review has shown that past EPA risk assessments overestimate PCB carcinogenicity.

Similar arguments could be made for other toxicity endpoints. Although the validity of a AHH receptor-mediated mechanism for coplanar PCBs is arguably a worthwhile area for toxicological research, the data simply cannot support a TEF scheme at this time.

One additional source of Panel concern is the recent Office of Research and Development "Dioxin Reassessment and Research" plan, Part B. It was our understanding that this program was targeted at incorporating recent mechanistic information on 2,3,7,8-TCDD biological activity, especially with regard to a receptor-mediated mechanism, into the EPA regulatory program for PCDDs and PCDFs. However, Part B focuses predominantly on development of in vivo TEFs for the coplanar PCBs and the measurement of TEQs in human serum samples. It is unclear how this information can assist the EPA in its reassessment of the risk of PCDDs and PCDFs, since, as discussed above, the toxicological data cannot at this time support the utilization of TEFs for PCBs in any regulatory scheme. Although research and data development may be an appropriate scientific exercise, any use of PCB TEFs in the dioxin risk reassessment program must be considered premature.

In summary, the Panels urge EPA to provide opportunity for internal and external review of the development and application of these TEF scheme for PCDDs and PCDFs. EPA should reconsider the introduction of TEFs for PCBs into risk assessment and regulatory schemes, at this time. PCBs are not dioxins and should be evaluated based upon the available data using sound scientific principles.

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