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Report to Congressional Requesters

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ENVIRONMENTAL HEALTH RISKS

Information on EPA's Draft Reassessment of Dioxins

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Abbreviations

CDD	polychlorinated dibenzo-*p*-dioxins
CDF	polychlorinated dibenzofurans
ED	effective dose
EPA	Environmental Protection Agency
IARC	International Agency for Research on Cancer
PCB	polychlorinated biphenyls
TCDD	2,3,7,8–tetrachlorodibenzo-*p*-dioxin
TEF	toxic equivalency factors
TEQ	toxic equivalency
USDA	Department of Agriculture
WHO	World Health Organization

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United States General Accounting Office
Washington, DC 20548

April 26, 2002

The Honorable John Breaux
The Honorable Thad Cochran
United States Senate

Some dioxins, which are chemical compounds that share certain structural and biological characteristics, have been linked to adverse human health effects, including cancer.[1] Often the byproducts of combustion and industrial processes, complex mixtures of dioxins enter the food chain and human diet through emissions into the air that settle on soil, plants, and water. The Environmental Protection Agency (EPA) and other entities, such as the World Health Organization, began assessing the potential human health risks of dioxins in the 1970s, when animal studies on one of them—2,3,7,8-tetrachlorodibenzo-*p*-dioxin, or TCDD—showed it to be the most potent cancer-causing chemical studied to date. EPA's initial assessment of dioxins was published in 1985. Since that time, there have been major advances in the scientific understanding of dioxin toxicity and significant new studies on dioxins' potential adverse health effects. As a result, in 1991 EPA decided to conduct a reassessment of the health risks of exposure to dioxins. A draft of this reassessment was reviewed by a scientific peer review panel in 1995, and three panels reviewed key segments of later drafts in 1997 and 2000.

EPA plans to release its comprehensive reassessment report on the health risks of dioxins this year. According to EPA officials, the report will conclude that dioxins may adversely affect human health at lower exposure levels than previously thought and that most exposure to dioxins occurs from eating such American dietary staples as meats, fish, and dairy products, which contain minute traces of dioxins. These foods contain dioxins because animals eat plants and commercial feed, and drink water, contaminated with dioxins, which then accumulate in animals' fatty tissue. EPA plans to use its reassessment of the risks posed by dioxins to develop a risk management strategy to address the health risks identified and to determine whether the nation's current air, water, and hazardous waste cleanup programs need to be changed to protect the public health. EPA's

[1]In this report, unless otherwise indicated, we use the term "dioxins" to refer to the three closely related families of chemical compounds (dioxins, furans, and polychlorinated biphenyls) that EPA evaluates in its reassessment of dioxins. In the scientific literature, these compounds may be referred to as "dioxins and dioxin-like compounds."

reassessment will be considered by the National Academies[2] in an ongoing study of the implications of dioxin in the food supply, which is examining, among other things, options to reduce dietary exposure to dioxins.

Of the several hundred known dioxins, 29 are considered toxic to varying degrees. TCDD is the most widely studied dioxin and one of the most toxic. EPA's reassessment report on the human health risks posed by dietary exposure to dioxins evaluates the health effects of TCDD and the 28 other compounds with similar structural and biological characteristics and varying toxic effects. According to EPA, its evaluation of the effects of these compounds is sufficient to characterize the effects of environmental dioxins in general.

Concerned about the potentially significant impact that EPA's dioxin risk assessment report could have on consumers and on the food and agriculture industries, you asked us to examine several aspects of EPA's reassessment of dioxins. As agreed with your offices, this report describes (1) the data EPA used to estimate human dietary exposure to dioxins in the United States; (2) how EPA's reassessment objectives, processes, analytical methods, and conclusions on the health risks posed by dioxins compare with those of the World Health Organization; and (3) the extent to which the draft dioxin reassessment report reflects the views of independent peer review panels that reviewed key aspects of the reassessment. Also as agreed with your offices, our report provides information on the relevant scientific issues but does not render an opinion on the scientific merits of the reassessment. This report is based primarily on EPA's draft reassessment report dated October 2001,[3] which EPA circulated for internal agency review, and on the two most recent peer reviews of key segments of the draft reassessment in 2000.

Results in Brief

EPA derived its estimates of human dietary exposure to dioxins in the United States from (1) various studies that chemically analyzed samples of 10 food types, (2) toxicity estimates of the various levels of the individual

[2]The National Academies consist of four organizations: the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine, and the National Research Council.

[3]The September 2000 draft reassessment report is posted on EPA's Web page. While the October 2001 draft reflects a number of revisions to the September 2000 version on the Web page in response to public and peer review comments, the drafts are substantially the same.

dioxins in these foods, and (3) estimates of the quantities of these foods consumed by Americans. To develop more reliable national estimates of dietary exposure, EPA incorporated into its analysis some food studies that were designed to be nationally representative. However, as EPA notes in its draft reassessment report, the food data were limited in several ways. In some cases, the food sampling methods, or the number of samples collected, were not sufficient to reliably estimate average, nationally representative exposures. In other cases, the studies did not analyze the food samples for the presence of all the dioxins that EPA was assessing. Further, most of the samples were collected 5 or more years ago; therefore, they may not reflect current exposures if, as EPA believes, emissions of dioxins have continued to decline in the United States since 1995 because of air quality regulations. Nonetheless, EPA believes that its estimate of average dietary exposure to dioxins is a reasonable characterization of current exposure because, for example, the emission reductions that have occurred since most of the food samples were collected are not believed to be as significant as earlier emission reductions. Regarding toxicity estimates, because sufficient data are not available on many of the individual dioxins, EPA used an approach that relies on data developed by the World Health Organization to estimate the toxicity of the various mixtures of dioxins identified in the 10 types of foods. Although this approach may overstate or understate the concentrations of dioxins in the foods, it is the internationally accepted scientific method for risk assessments of dioxins.

While both EPA and the World Health Organization have taken steps during the past decade directed at the general objective of assessing the human health risks of dioxins, some of their specific objectives and processes have differed. Nonetheless, the analytical methods the organizations used and the conclusions they reached have much in common. EPA established a long-range objective of characterizing the potential human health risks posed by exposure to dioxins using a comprehensive, multiyear review process resulting in a reassessment report. In contrast, the World Health Organization conducted a series of individual reviews with more narrowly focused primary objectives, such as updating the estimated amount of dioxins to which a person could be exposed daily for a lifetime without appreciable health consequences. Regarding analytical methods and conclusions, both EPA and the World Health Organization:

- Examined similar sets of human and animal study data, considered a similar range of health effects, and applied some analytical concepts that

both entities determined were more appropriate to the assessment of dioxins than those often used in assessments of other chemicals.

- Concluded that dioxins could adversely affect human health at lower exposure levels than previously thought and that some adverse noncancer effects, such as reproductive and developmental impairments, could occur at or near the levels to which the general population is now being exposed.

A major difference in the organizations' assessments concerns whether there are threshold levels below which exposure to dioxins would pose a negligible risk of cancer. While EPA assumed there is no safe threshold level for cancer effects, the World Health Organization assumed there is.

EPA's draft reassessment report largely reflects the recommendations and suggestions provided to the agency by the two most recent independent peer review panels, although some areas of disagreement on key scientific issues remain. The panels, one consisting of 12 independent reviewers and the other convened by EPA's Science Advisory Board, concurred with many key assumptions and approaches that EPA used. In addition, the panels made recommendations on several issues and provided suggestions for EPA to consider. EPA generally addressed the panels' recommendations and suggestions by, for example, performing additional analyses or explaining that the data currently available are not yet sufficient to address the recommendation or suggestion. If EPA disagreed with the panels' recommendations or suggestions, it explained its position in the text. Additional changes are being made as EPA prepares the draft for external interagency review. Lack of consensus on some scientific issues, such as whether the weight of evidence supports EPA's classification of TCCD as a human carcinogen, reflects uncertainty in areas where data are limited. Accordingly, the Science Advisory Board views this reassessment report as an interim evaluation that will need to be updated and peer reviewed in the future as important data gaps are addressed.

Background

Dioxins persist for a long time in the environment because they do not dissolve in water and are relatively immobile in soil and sediment. When animals consume plants, feed, and water contaminated with dioxins, they accumulate in the animals' fatty tissue. Similarly, when humans consume these animals, the dioxins then accumulate in human fatty tissue. According to EPA, because dioxins also persist in the body for years, recent significant reductions in dioxin emissions into the air are unlikely to reduce human health risks in the near term.

While EPA estimates that most exposure to dioxins occurs from eating commonly consumed foods, the draft reassessment report also estimates that limited exposure to dioxins results from breathing air containing trace amounts of dioxins; inadvertently ingesting soil containing dioxins; and absorbing through the skin minute levels of dioxins present in the soil. Some people may experience higher exposure levels than the general population as a result of food contamination incidents; workplace exposures; industrial accidents; or consuming unusually high levels of fish, meat, or dairy products. When calculating human exposures, dioxins are measured in picograms—that is, trillionths (0.000000000001) of a gram. Highly sophisticated measurement techniques and technologies are required to test foods for the presence of the 29 dioxins identified as having toxic effects.

The several hundred known dioxin compounds can be placed in one of three closely related families: polychlorinated dibenzo-*p*-dioxins (CDD), polychlorinated dibenzofurans (CDF), and polychlorinated biphenyls (PCBs). CDDs and CDFs are byproducts of combustion and some industrial processes. According to EPA, U.S. emissions of CDDs and CDFs into the environment declined by 75 percent between 1987 and 1995 primarily as a result of reductions in emissions from municipal and medical waste incinerators. Some PCBs share certain characteristics with CDDs and CDFs and therefore are identified as "dioxin-like." PCBs were at one time manufactured for use in products such as lubricants and industrial transformers but have not been made in the United States since 1977. However, because dioxins break down so slowly, past emissions remain in the environment for years—even decades—before they diminish. Consequently, a large part of humans' current exposure to dioxins is due to releases of dioxins that were stored in soil and sediment, and to a lesser extent in vegetation and the atmosphere. These sources are called "reservoir sources." EPA believes that with the reduction in current emissions from combustion and incineration, these reservoir sources have taken on more significance.

According to EPA, dioxins always occur in the environment and in humans as complex mixtures of individual compounds. However, the complex nature of the dioxin mixtures to which people are exposed (through foods or other sources) complicates evaluation of the health risks such mixtures might pose. Scientists therefore developed the concept of toxic equivalency factors (TEFs) to facilitate risk assessment of exposure to these mixtures. Because TCDD is the best-understood dioxin, it is used as a frame of reference for estimating the toxicity of the other dioxins, and its TEF is set at 1.0. Only 1 of the other 28 dioxins included in

EPA's reassessment has a TEF of 1.0; most of the others have TEFs of 0.1 or less, meaning that they are considered less toxic to humans than TCDD. International experts review and periodically update the TEFs based on new data. For its reassessment of dioxins, EPA used the latest revisions that were made at an expert meeting organized by the World Health Organization in 1997.[4]

Since 1991, EPA has been updating its initial 1985 report assessing the health risks of dioxins. The October 2001 draft reassessment report exceeds 3,000 pages. Part I of the draft report provides information on exposure to dioxins, including chapters on dietary intake; part II addresses health assessment methodologies and specific health effects; and part III, the *Integrated Summary*[5] highlights information in parts I and II on exposure and health effects and provides a risk characterization—a statement summarizing EPA's assessment of the health risks associated with dioxins. In the reassessment, EPA studied the risks of cancer as well as noncancer health effects, such as neurological and reproductive impairments.

Founded in 1948, the World Health Organization (WHO) is a specialized agency of the United Nations, with 191 member states. WHO's functions include giving worldwide guidance in the field of health and setting global standards for health. WHO carries out these functions through a variety of offices and programs that often collaborate with each other and with other public health entities of WHO's member states and nongovernmental organizations. The principal contributors to the WHO reassessments of dioxin risks that are discussed in this report have been (1) the International Agency for Research on Cancer, which coordinates and conducts both epidemiological and laboratory research into the causes of cancer; (2) the WHO European Centre for Environment and Health, which coordinates comprehensive efforts, in collaboration with the International Programme on Chemical Safety, to evaluate the possible health risks of dioxins as well as methods of prevention and control of environmental

[4]The World Health Organization (WHO) met in Stockholm in June 1997 to update earlier TEFs on dioxins for human risk assessment. As of 2002, both EPA and WHO use the TEFs adopted by WHO in 1997, and published by Van den Berg et al. in 1998.

[5]The full title of part III is *Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds.*

exposure of the general population to these chemicals;[6] and (3) the Joint Expert Committee on Food Additives of the United Nations' Food and Agriculture Organization and WHO, which provides scientific evaluations as a basis for the development of food standards by the Codex Alimentarius (food code) Commission.[7]

EPA Used Data on the Presence of Dioxins, Toxicity, and Food Consumption to Estimate Human Dietary Exposure

To estimate dietary exposure to dioxins, EPA obtained and reviewed information on (1) the dioxins present in 10 types of foods[8] with high fat content, (2) the toxicity of individual dioxins contained in these food types, and (3) the quantities of these foods that people in the United States typically eat. EPA has incorporated new studies following improvements in analytical capabilities to detect dioxins in food during the 1990s. However, in its draft reassessment report, EPA identified a number of limitations with the food data used to estimate dietary exposure that add uncertainty to the agency's overall estimate of current average daily dietary exposure to dioxins. For example, in some cases, the studies available on the presence of dioxins in foods were not designed to estimate national averages. Further, while EPA used the accepted method for estimating the toxicity of the dioxins found in the 10 food types, EPA and others acknowledge that the method has limitations. Finally, EPA estimated the quantities of these foods consumed using U.S. Department of Agriculture (USDA) data on U.S. adults' food consumption based on surveys made between 1989 and 1991; however, EPA believes the dietary habits of Americans have changed very little over the course of the past decade.

[6]The International Programme on Chemical Safety, established in 1980, is a joint program of three cooperating organizations: the United Nations Environment Programme, the International Labour Organisation, and WHO. The International Programme on Chemical Safety's main roles are to establish the scientific basis for safe use of chemicals and to strengthen national capabilities and capacities for chemical safety.

[7]The Food and Agriculture Organization of the United Nations was founded in 1945 with responsibilities covering nutrition and associated international food standards. Among its activities, the Organization approves international standards and helps frame international conventions and agreements.

[8]EPA's *Integrated Summary* (table 4-7) presents information on exposures to 9 foods, while the detailed exposure chapters, chapters 3 and 4, present information on 10 foods. However, the estimated total exposures from foods in both parts of the reassessment are almost identical.

EPA Estimates That Most Human Exposure to Dioxins Occurs from Eating Certain Types of Foods

A body of scientific research on foods in Europe, North America, and other locations indicates that the primary source of human exposure to dioxins is the dietary intake of foods, especially those containing animal fat. According to EPA's October 2001 draft reassessment report, the average adult in the United States receives about 95 percent of his or her exposure to dioxins by eating commonly consumed foods, such as beef, pork, and poultry; fish; and dairy products. (EPA estimated small exposures to dioxins from the air and soil as well.)

The 10 types of foods EPA analyzed for its reassessment are beef; pork; poultry; other meats, such as lamb and baloney; eggs; milk; dairy products, such as cheese and yogurt; freshwater fish and shellfish; marine fish and shellfish; and vegetable fat, such as corn and olive oils and margarine. These foods, only one of which is not of animal origin, are believed to be the major contributors to dietary exposure to dioxins. Even though vegetable fat products are estimated to contain low levels of dioxins, EPA included these foods in its analysis because they are high in fat and common in the American diet. EPA excluded fruits and vegetables from its analysis because data on dioxins in U.S. fruit and vegetable products, which generally contain little or no fat, are extremely limited. The existing data indicate that typically these products contain low levels of dioxins, which generally stem from residues—deposits on outer layers with little penetration to inner portions.

Until recently, chemical analyses of dioxins in foods have focused primarily on two of the families of dioxins, the CDDs and CDFs, with less attention on identifying and measuring specific PCBs. The draft reassessment report includes an evaluation of PCB levels in the 10 food types. The draft report identifies estimated exposures to CDDs and CDFs together and identifies the estimated exposure to PCBs separately. This approach provides information that can inform potential regulatory approaches, among other things, because CDDs and CDFs result primarily from combustion and industrial processes, whereas PCBs, which persist in the environment from the 1970s and earlier, are no longer being manufactured.

As shown in table 1, EPA estimated that the average adult in the United States is exposed daily to about 63 picograms of dioxins through dietary intake, with the highest exposure coming from beef and freshwater fish and shellfish. According to EPA, this exposure level is close to the level that has caused adverse noncancer effects in animals, such as effects on the development of reproductive systems. It is important to note that EPA's dietary exposure estimates are averages, and they do not apply to

adults with additional or unusual exposure to dioxins—for example, from diets unusually high in fat content or diets of foods high in dioxin content.[9]

Table 1: EPA's Estimates of the Average U.S. Adult's Daily Exposure to Dioxins From Dietary Intake, Picograms per Day

Food type	Dietary exposure to CDDs and CDFs	Dietary exposure to PCBs	Total dietary exposure to dioxins
Beef	9.0	4.2	13.2
Freshwater fish and shellfish	5.9	7.1	13.0
Dairy products (cheese, yogurt, etc.)	6.6	3.2	9.8
Other meats (lamb, baloney, etc.)	4.5	1.0	5.5
Marine fish and shellfish	2.5	2.4	4.9
Milk	3.2	1.5	4.7
Pork	4.2	0.2	4.4
Poultry	2.4	0.9	3.3
Eggs	1.4	1.7	3.1
Vegetable fat (oils, margarine, etc.)	1.0	0.6	1.6
Total	**40.7**	**22.8**	**63.5**

Notes: The average adult is assumed to weigh 70 kilograms (154 pounds). A picogram is one-trillionth of a gram.

Source: Derived from U.S. EPA, October 2001 draft dioxin reassessment report, chapter 4, tables 4-30 and 4-31.

The Food Samples EPA Studied to Identify the Presence of Dioxins Had a Variety of Limitations

To estimate any population's dietary intake of dioxins, the specific dioxins present in the various foods must be identified and measured through chemical analyses of the foods. However, reliable estimates of the average concentrations of dioxins in specific foods nationwide have only recently begun to be available. In the past, data were available only from studies of dioxin concentrations in a specific food product or products in a specific location or a few locations, and these data were not sufficient to reliably estimate average national exposure. During the 1990s, as analytical capabilities to detect dioxins at parts-per-trillion levels were developed, new studies of foods in the United States, some with broader scope than the earlier studies, became available. EPA has incorporated new studies

[9]The reassessment report addresses variability in general population exposure, indicating it results primarily from differences in dietary choices that individuals make. EPA estimates that dietary intake of dioxins for the general population may extend to levels two to three times higher than the mean estimate.

into its analysis of dietary exposure to dioxins to try to develop more reliable national estimates of such exposure. As a result, the estimates presented in the October 2001 draft reassessment report are based on more food data than the drafts developed just a few years ago.

Nevertheless, in its October 2001 draft reassessment report, EPA said that the amount and the representativeness of the food data it used to estimate the average U.S. adult's dietary exposure to dioxins vary. Further, EPA officials acknowledged that some of the available studies were not designed to estimate national average exposures. As discussed below, the food sample data are limited in part by the timing of the sampling, variations in the methods used to collect the samples, and the types of samples collected and analyzed. In commenting on a draft of this report, EPA officials said that these food data limitations do not represent major weaknesses in its estimates of dietary exposure to dioxins.

- As reported in the draft reassessment, most of the food samples were collected between 5 and 8 years ago. Current samples would be expected to have lower dioxin levels because emissions containing dioxins declined by about 75 percent from 1987 to 1995, and EPA believes the downward trend is continuing.[10] Nevertheless, EPA believes that the exposure estimates based on food data from the mid-1990s are representative of current dietary exposure for several reasons. First, EPA believes that because most of the food samples the agency used for its reassessment were collected after the 75-percent decrease in emissions, much of the decrease should already be reflected in the foods' dioxin concentration numbers. Second, EPA said that, because most municipal and medical waste incinerators are located far from and downwind of concentrated meat and dairy production areas, the impact of any emission reductions since 1995 on the commercial food supply should be proportionately less than on the environment in general. Third, EPA said that because reservoir sources of dioxins account for half or more of current exposure, and because some sources of dioxins are unknown, it is unlikely that emission reductions that occurred after most of the food samples were taken would significantly affect the current estimate of general population exposure from the commercial food supply.

[10]EPA does not have information on dioxin emissions reductions post-1995. However, EPA's air toxics regulations are expected to result in further reductions. For example, EPA expects that its 1995 air toxics rule for large municipal waste combustors—associated with more than 60 percent of total dioxin emissions—and its 2000 air toxics rule for small municipal waste combustors will reduce dioxin emissions from these entities to less than 1 percent of 1990 levels.

- According to EPA, while its analyses of some of the foods are based on national samples collected from food processing or food monitoring locations, such as federal slaughtering establishments, other analyses are based on limited "market basket surveys"—random purchases of selected products, such as eggs, direct from grocery stores—in a small number of U.S. and Canadian cities.[11] Depending on their design, national surveys would generally be more representative of average dietary exposures to dioxins than limited surveys.
- Some of the analyses of the foods were derived from individual food samples, while others were from composite samples. Using composites is more economical than using individual samples, and EPA believes they are appropriate for use in analyzing dioxin concentrations to establish average, or mean, exposure estimates. However, EPA acknowledges that data on the variability or range of results from individual samples typically are not available from studies analyzing composite samples. As a result, information that can provide insight into the reliability of the estimates is not available. Table 2 shows the number(s), type(s), and date(s) of the samples EPA used for each of the 10 food categories.

[11]Some of the market basket surveys cited by EPA were conducted under the auspices of the Food and Drug Administration.

Table 2: Numbers, Types, and Dates of Food Samples EPA Used in Estimating Dietary Exposure to Dioxins

Food type	Number/type of sample	Year(s) samples collected
Beef (back fat samples)	63 individual samples	1994
Pork (belly fat samples)	78 individual samples	1995
Poultry (abdominal fat samples)	78 individual samples	1996
Milk	8 composite samples	1996 and 1997
Dairy products	8 composite samples	1996 and 1997
Eggs[a]	15 composite samples (24 eggs each)	1997
Marine fish and shellfish[a]	158 individual samples	1995 and 1996
Freshwater fish and shellfish[a]	222 samples (individual and composite)	1986-89; 1994; 1996-99
Vegetable fat (oils, margarine, etc.)[a]	30 individual samples	1995[b]
Other meats	[c]	[c]

[a]EPA used these samples to analyze CDDs and CDFs only.

[b]Estimate based on 1996 study publication date.

[c]EPA did not provide this information for other meats.

Source: U.S. EPA, October 2001 draft dioxin reassessment report.

- According to the draft reassessment report, data from some of the food studies were sufficient to estimate exposure to total dioxins—the CDDs, CDFs, and PCBs. However, the report shows that in other cases, the data only provided support for estimating exposure to CDDs and CDFs. As a result, for four food categories, different studies are used for estimating exposure to CDDs and CDFs than those used for PCBs. As reported in the draft reassessment, these studies analyzed fewer samples, a number of which were collected 14 or more years ago and therefore provide data on dioxins that may not reflect current levels. Table 3 shows information on the four foods for which EPA used different samples to estimate exposure to PCBs than those used to estimate CDDs and CDFs.

Table 3: Numbers, Types, and Dates of Food Samples EPA Used in Estimating Dietary Exposure to PCBs in Four Food Categories

Food type	Number/type of sample	Year(s) samples collected
Eggs	18 individual samples	1995
	6 composite samples[a]	1986-88[b]
Marine fish and shellfish	1 composite of 13 samples	1995
	5 composites[a]	1986-1988
Freshwater fish and shellfish	1 composite of 10 samples	1995
	6 composites[a]	1986-88[b]
Vegetable fat	5 composites[a]	1986-88

[a]The studies used in the analyses do not specify the number of individual samples in the composite samples.

[b]The year that one of the composite samples was collected is not identified. The study was published in 1989.

Source: U.S. EPA, October 2001 draft dioxin reassessment report.

- As EPA acknowledges in the draft report, its analyses of dioxins present in foods are based on uncooked foods, even though dioxin levels can be different in cooked and uncooked foods. According to EPA, while many studies indicate that foods have similar dioxin concentrations whether they are cooked or uncooked, the studies show that some foods have lower concentrations of dioxins when they are cooked, while others have higher levels when they are cooked. These differences reflect, in part, the fact that different cooking methods (frying, boiling, grilling, etc.) may have different effects on dioxin levels. On the basis of the available data, which it believes are not conclusive, EPA states in the draft reassessment report that uncooked food is a reasonable surrogate to use for identifying and quantifying dioxin concentrations in cooked food.
- Because the primary focus of EPA's exposure assessment was on foods produced and consumed in the United States, EPA's analysis does not address imported food products that may vary from domestic sources in dioxin content.

Despite these limitations, the data on dioxin levels in foods supporting the October 2001 draft report reflect a significant improvement compared with the data EPA had available for use in its 1994 draft reassessment report, which was peer reviewed in 1995 by EPA's Science Advisory Board. Specifically, in the 1994 draft, EPA provided estimates of levels of CDDs and CDFs for seven food types; the October 2001 draft provided estimates for ten food types. With the exception of an estimate for fish that was

based on 60 samples, the 1994 draft estimates were developed from samples ranging in number from 2 to 14; as table 2 shows, the number of samples used for the 2001 draft is greater. In addition, while EPA recognized that PCBs were being identified in foods, the agency did not have sufficient data at that time to develop estimates of the levels of specific PCBs in foods; the 2001 draft does include estimates of PCB levels in foods.

The following sections describe in greater detail the samples EPA used to identify the level of dioxins in 9 of the 10 foods studied—beef, pork, and poultry; freshwater and marine fish; milk, dairy, and eggs; and vegetable fat—and any associated limitations or uncertainties. (The draft reassessment report does not provide any information supporting EPA's estimate of the types and amounts of dioxins in other meats, the tenth food type.[12] In commenting on a draft of our report, EPA said that information on other meats would be provided in its final report.)

Beef, Pork, and Poultry

In estimating exposure to dioxins from beef, pork, and poultry, EPA used data from the first statistically designed national surveys of dioxin levels in these foods sponsored by EPA and USDA. These surveys were designed to be representative of all U.S. regions and all classes of animals slaughtered in federally inspected slaughtering establishments. EPA believes the three surveys provide reasonable estimates of the average national concentrations of dioxins in beef, pork, and poultry. Nonetheless, information EPA provided in the draft reassessment report about these samples identifies some limitations and uncertainties about these studies.

- The samples are now between 6 and 8 years old and therefore may not reflect current exposures. To address this data gap, EPA and USDA are conducting a follow-up study on dioxin levels in beef, pork, and poultry that will commence in 2002 and provide updated information. However, EPA officials said the results of this survey will likely not be available for incorporation into the dioxin reassessment report that EPA plans to publish this year.
- The animal samples for beef, pork, and poultry were not meat products sold in grocery stores but rather were cuts of fat generally not consumed—either back fat, abdominal fat, or belly fat from slaughtering

[12]The report's references to this category of food are limited to several tables in the chapters on dietary exposure in which the estimates are provided, while the *Integrated Summary* cites nine foods, excluding other meats.

establishments. Some uncertainty therefore surrounds the accuracy of EPA's estimates of dietary intake of dioxins because of comparability concerns. EPA used this approach because USDA federal inspectors could obtain the samples with little disruption to the slaughtering establishments and because the samples' high fat content would enable more accurate measurement of dioxins, since the analysis would be of highly concentrated fat samples. However, this approach assumes that edible meat products sold in grocery stores contain the same types and amounts of dioxins as the fat samples (adjusted for differences in percentages of fat). According to EPA, this assumption is supported by a well-developed understanding of the manner in which dioxins distribute across fat reservoirs in vertebrates. Therefore, EPA concluded that the fat samples for all three foods were comparable to the edible meat samples. EPA also based its conclusion on its analysis of beef samples—comparing five back fat samples with other cattle parts, including muscle tissue, which could be representative of edible beef products.[13] For the five samples, the ratios of CDDs and CDFs in muscle fat to CDDs and CDFs in back fat varied by up to 300 percent, ranging from 0.58 to 1.7; and the ratios for PCBs varied by up to 50 percent, from 1.0 to 1.5.[14] Although some of the variation may result from imprecision inherent in measuring picograms, this limited analysis indicates that using fat samples may overstate or understate to some extent the dioxin levels in beef, pork, and poultry products.

- EPA reported that it excluded 2 of the 80 samples of abdominal fat from poultry because they had significantly higher concentrations of certain dioxins than the other samples. EPA, USDA, and the Food and Drug Administration investigated the cause of these elevated dioxin levels and determined that it stemmed from contaminated animal feed that had been distributed to poultry, fish, hog, and cattle producers in several southern and southwestern states.[15] EPA considered the two poultry fat samples inappropriate for the dioxins study, which was aimed at identifying typical exposures to dioxins. However, it is not clear that the poultry samples with high concentrations of dioxins were anomalies because the incidence

[13]U.S. Environmental Protection Agency, Matthew Lorber et al, *Distribution of Dioxins, Furans, and Coplanar PCBs in Different Fat Matrices in Cattle (*Washington, D.C., 1997).

[14]EPA also excluded other beef samples from its analysis on the basis that the source animals had unusually high levels of dioxin exposure. However, the analysis does not explain why the ratios (and thus the overall comparability) would vary with levels of exposure.

[15]U. S. General Accounting Office, *Food Safety: Agencies' Handling of a Dioxin Incident Caused Hardships for Some Producers and Processors*, GAO/RCED-98-104,Washington, D.C.: Apr. 10, 1998).

of dioxin contamination in animal feeds is not known. For example, this instance of contaminated animal feed was discovered by the first national poultry sample, which tested only 80 samples nationwide.

- In response to suggestions from a peer review panel, when the data were sufficient to do so, EPA presented a standard deviation—the typical amount of variability around the mean—on its estimates of the average levels of dioxins in the foods, as well as the range of the levels of dioxins identified in the samples. For beef, pork, and poultry, EPA was able to provide this information for the CDDs and CDFs. These data indicated considerable variability in the levels of CDDs and CDFs in the foods. For example, the estimated level of 0.28 picograms of dioxins in a gram of pork has a standard deviation of plus or minus 0.28. In other words, the standard deviation is equal to or greater than the mean. Accordingly, the estimated dioxin level is subject to a wide range of uncertainty.
- Because EPA did not have sufficient information to develop a standard deviation for PCBs, the agency could not develop a standard deviation for total dioxins (the combination of CDDs, CDFs, PCBs) in beef, pork, and poultry. As a result, EPA could not state with any degree of certainty that exposure to total dioxins or to PCBs would fall within specified levels. EPA believes this limitation is a minor one because it considers the average exposure level, rather than the more limited extreme exposures, to be of greater public health interest. Nonetheless, this additional analysis, if available, would enable policymakers, scientific peer reviewers, and other users to better evaluate the extent to which the data may be representative of average national exposures.

Freshwater and Marine Fish and Shellfish

Though EPA analyzed more fish samples for the current reassessment draft than for earlier drafts, the current draft report acknowledges that the levels of dioxins in fish are more uncertain than those in the other foods for two reasons. First, the data lack the "geographic coverage and statistical power" of the other food surveys. That is, while the sample sizes for CDDs and CDFs in fish are considerably larger than those used for the analyses of other foods, they do not provide data that are nationally representative because of the diversity of fish and bodies of water. Specifically, there are a significant number and variety of freshwater and marine fish species living in numerous bodies of water that contain differing types and levels of dioxins. Moreover, fish consumed in the United States include both farm-raised and wild fish. Second, EPA based its estimates for levels of PCBs in fish on a much smaller data set than it used for CDDs and CDFs. EPA used 222 samples to estimate the levels of CDDs and CDFs in freshwater fish and shellfish and 158 samples for marine fish and shellfish compared with 7 and 6 composite samples for PCBs for freshwater and marine fish, respectively. Further, most of the

samples for PCBs were from Canadian rather than U.S. cities, and the analyses of levels of PCBs in them did not evaluate all of the PCBs identified as being toxic. For example, according to the report, only one of the composite samples for marine fish and shellfish, collected between 1984 and 1986, was analyzed for the presence of the most common and toxic PCB, referred to as PCB-126. For these reasons, EPA acknowledges in the draft report that the resulting estimates are not representative of the level of dioxins in fish nationally. We note that the limitations of the data used to estimate the levels of PCBs in fish are particularly significant because in the report, EPA estimates that freshwater fish contains the highest levels of PCBs (and total dioxins) of all the foods studied.

The samples EPA used to estimate the levels of dioxins in fish were derived from EPA's National Bioaccumulation Study[16] and three market basket surveys in the United States and Canada. Samples for the bioaccumulation study were collected between 1986 and 1989, whereas the samples for the market basket surveys were collected about a decade later, between 1995 and 1999. Some of the limitations and uncertainties associated with these samples that EPA acknowledged in the draft report are highlighted below.

- Most of the fish samples used for the reassessment draft were collected 5 or more years ago; some are between 13 and 16 years old.
- EPA did not have sufficient data to estimate exposure to PCBs from eating freshwater or marine shellfish.
- Some of the estimates for freshwater fish, such as trout, are based on samples from the bioaccumulation study that may be more representative of wild fish (i.e., fish caught in recreational fishing) than fish typically purchased by the general population at grocery stores, which is largely farm-raised. Specifically, in cases in which EPA did not have data on farm-raised freshwater fish or fish purchased in grocery stores, the agency used the concentration of CDDs and CDFs from samples of wild caught fish from the bioaccumulation study. This use of older data on wild fish increases the uncertainty about the representativeness of EPA's exposure estimate.
- For some fish species, such as mullet and mackerel, estimates were based entirely on samples collected in the Mississippi area and therefore may not be representative of levels seen in other locations.

[16]EPA's National Bioaccumulation Study, published in 1992, investigated the prevalence of selected bioaccumulative pollutants, including dioxins, in fish.

- EPA did not have sufficient data to estimate a standard deviation for the average levels of dioxins in freshwater or marine fish. As a result, EPA cannot state with any degree of certainty what the related dietary exposure to dioxins is.

Milk, Dairy, and Eggs

The milk samples upon which both the milk and dairy estimates are based came from a national survey. In this survey, samples were collected during the four seasons, providing information on seasonal (temporal) variations. The milk samples were collected from 51 sampling stations, located in a majority of the states, that support EPA's Environmental Radiation Ambient Monitoring System.[17] In contrast, the estimates for CDDs and CDFs in eggs are based on Food and Drug Administration market basket surveys in 1997 in California, Georgia, Minnesota, New York, Ohio, Oregon, Pennsylvania, and Wisconsin. The estimates for PCBs in eggs are based on market basket surveys in San Diego, California; Atlanta, Georgia; Binghamton, New York; and five major Canadian cities. EPA used composite samples of milk and eggs to identify and measure the presence of specific dioxins in milk, dairy, and eggs. Information provided in the draft report identifies some limitations associated with these data.

- Most of the milk samples were collected 6 years ago.
- The egg samples used to support the analyses for CDDs and CDFs were collected 5 or more years ago. The estimates for PCBs in eggs are based, in part, on samples obtained in five Canadian cities between 14 and 16 years ago.
- Only one of the six composite samples used to estimate the level of PCBs in eggs was analyzed for the presence of the most common and toxic PCB.

Vegetable Fat

According to EPA, its estimates of CDDs and CDFs in vegetable fat were developed from a market basket survey that was not representative of edible oil consumption in the United States. The 30 samples of various oils, solid shortening, margarine, and an oil spray were obtained from grocery stores in nine U.S. cities or metropolitan areas: Chicago, Illinois; Cincinnati, Ohio; Denver, Colorado; Miami, Florida; Minneapolis, Minnesota; Salt Lake City, Utah; San Antonio, Texas; San Francisco, California; and the Washington, D.C., metropolitan area. Although neither the reassessment report nor the study (published in 1996) states when the

[17]EPA's Environmental Radiation Ambient Monitoring System is a national network of monitoring stations that regularly collect air, water, precipitation, and milk samples for analysis of radioactivity. The samples were collected from 51 stations located in 41 states, Puerto Rico, and Panama.

samples were collected, there is typically at least a 1-year lag between collection and publication, indicating that the samples were collected 8 or more years ago. EPA used limited data to estimate the level of PCBs in vegetable fat. This estimate is derived from five composite samples of cooking fats and salad oils, each of which was obtained 14 or more years ago from one of five major (unidentified) Canadian cities. As a result of these limitations that EPA identified in the draft report, the estimate for dietary exposure to dioxins from eating vegetable fats is unlikely to reflect current average dietary exposure in the United States.

Method EPA Used to Estimate Toxicity of Dioxins in the 10 Food Types Is Accepted by Experts but Has Limitations

After using the chemical analyses discussed previously to identify the types and quantities of dioxins present, EPA estimated the toxicity of the dioxins in the 10 types of foods, using measures called toxic equivalency factors. (As noted earlier, these measures—called TEFs—are used to create a frame of reference by comparing the potential toxicity of individual dioxins in a sample with the toxicity of the most toxic and best understood dioxin, TCDD, which is assigned a TEF of 1.) EPA used the TEFs that were updated by WHO in 1997. For each of the types of foods, EPA multiplied the measured types and amounts of the dioxins present by the related TEFs to arrive at a "dioxin toxic equivalence value" for that particular food category/dioxin combination.[18] For each food category, the total dioxin toxic equivalency is the sum of these products—that is, the sum of the toxic equivalence values for (1) CDDs and CDFs and (2) PCBs. This provides an indicator of the relative toxic concentration of dioxins in each food category. As table 4 shows, EPA estimated that freshwater fish and shellfish had the largest per-gram concentration of dioxins with toxic effects.

[18] For beef, pork, poultry, milk, and dairy products, the toxic concentrations are also based on EPA's estimates of the average percentage of fat in these foods--17, 19, 9, 1.8, and 12 percent, respectively.

Table 4: EPA's Estimates of Toxic Concentrations of Dioxins in 10 Food Categories, Picograms per Gram

Food category	Dioxin toxic equivalence values for CDDs and CDFs	Dioxin toxic equivalence values for PCBs	Total dioxin toxic equivalence values
Freshwater fish and shellfish	1.00	1.20	2.20
Marine fish and shellfish	0.26	0.25	0.51
Pork	0.28	0.01	0.29
Beef	0.18	0.08	0.26
Other meats	0.18	0.04	0.22
Eggs	0.08	0.10	0.18
Dairy	0.12	0.06	0.18
Poultry	0.07	0.03	0.10
Vegetable fats	0.06	0.04	0.10
Milk	0.02	0.01	0.03

Note: The toxic equivalence values are estimated on a whole (wet) weight basis, as opposed to a dry weight basis.

Source: Derived from U.S. EPA, October 2001 draft dioxin reassessment report.

The toxic equivalence approach using TEFs has evolved over the last 20 years and is the internationally accepted scientific approach for risk assessments of dioxins. This approach has been formally adopted by several countries and as guidance by international organizations, such as WHO. TEFs are used to decrease the overall uncertainty in assessing the health risks of dioxins because they provide a framework for addressing the complex mixtures of dioxins to which people are most often exposed. Nonetheless, a number of uncertainties are involved in the use of the TEF concept. As a result of these uncertainties, estimates of the concentrations of dioxins in foods based on this approach may be overstated or understated.

The draft reassessment report acknowledges that there are still many questions about the use of the TEF method and the validity of some of the underlying assumptions. The report states that many assumptions are necessary because of lack of data. Specifically, the derivation of TEFs is limited by the amount of available data on the relative potency of different dioxins compared with TCDD. For many dioxins, the available data on relative potency may be limited to only a few experimentally observed effects. Some of these effects may not be considered toxic by themselves, but they still might provide evidence that exposure to dioxins led to biological or chemical effects in experimental subjects. For example, EPA noted that only TCDD and one mixture of certain dioxins have been tested

for carcinogenicity. Therefore, in order to develop a TEF that estimates the cancer potency of a mixture including other dioxins, scientists have assumed that the relative potencies observed for noncancer effects approximate those for cancer. In other words, once derived, TEFs apply to all effects, not just those for which relative potency data were available.

Nonetheless, after considering a number of the uncertainties and limitations of this approach, the international experts who derived the current TEFs concluded that the TEF concept is still the most plausible and feasible approach for risk assessment of dioxins. Furthermore, the TEF values for individual dioxins are reevaluated and updated periodically to reflect the available evidence. When WHO established the most recent TEFs in 1998, it suggested that the toxic equivalency scheme be reevaluated every 5 years and that the TEFs and their application to risk assessment be reanalyzed to account for emerging scientific information.

Daily Dietary Intake Estimates Are Primarily Based on Food Surveys of U.S. Adults Administered Between 1989 and 1991

To develop its estimate of the daily dietary intake of dioxins by the average adult in the United States, EPA needed to calculate the amount of food containing dioxins that Americans typically eat. EPA obtained this information for the 10 food types from USDA food intake surveys. The USDA survey data include information on the amounts of specific foods consumed in a day by an average person weighing 70 kilograms (154 pounds).

USDA obtained its data from detailed food surveys prepared by thousands of individuals selected from statistical samples. In these surveys, individuals generally provided detailed information on food consumption for 2 days. The surveys used statistical sampling to ensure that all seasons, geographic regions of the United States, and demographic and socio-demographic groups were represented. EPA's analysis of these data tabulated intake rates for the major foods, as well as for individual food items. The total quantity of each food eaten by the survey population in a survey day was tabulated and weighted to represent the quantity eaten by the entire U.S. population in a typical day. For the draft reassessment report, EPA averaged USDA's data for three age groups of adults ranging from ages 20 to 70 and over. Table 5 provides EPA's estimates of the daily dietary intake of 10 food types by adults in the United States.

Table 5: Estimated Daily Dietary Intake of 10 Food Types for an American Adult Weighing 70 Kilograms (154 pounds)

Food	Estimated dietary intake (grams per day)
Milk	175.0
Dairy	55.0
Beef	50.0
Poultry	35.0
Other meats	25.0
Eggs	17.0
Vegetable fats	17.0
Pork	1.5
Marine fish and shell fish	9.6
Freshwater fish and shellfish	5.9

Source: Derived from U.S. EPA, October 2001 draft dioxin reassessment report.

While EPA prefers to use USDA food data from the 1989-91 USDA *Continuing Survey of Food Intake By Individuals* because it has conducted a statistical analysis of these data and includes them in the agency's *Exposure Factors Handbook*,[19] the draft reassessment report uses other data for fish and does not provide information on the basis for its estimates of dietary intake of other meats. Specifically, the draft reassessment report derived its estimates of the daily dietary intake of beef, pork, poultry, milk, dairy products, vegetable fats, and eggs from USDA's *Continuing Survey Food Intake By Individuals* conducted from 1989 through 1991. In contrast, the daily dietary intake of freshwater and marine fish and shellfish were derived from a March 2000 report on the consumption of fish prepared by EPA's Office of Water. This report used data from USDA's *Continuing Survey of Food Intakes By Individuals* conducted in 1994, 1995, and 1996. In this report, EPA weighted its estimates of exposure to dioxins from fish by the species-specific concentrations according to species-specific fish consumption rates for the U.S. population. However, in cases where species-specific concentration data were not available, EPA used default values. For example, EPA used data from the bioaccumulation study as the default for

[19]EPA's August 1997 *Exposure Factors Handbook* provides data on standard factors needed to calculate human exposure to toxic chemicals, including the estimated average daily intake of foods that EPA program offices are encouraged to use in exposure assessment activities.

certain freshwater fish. The use of various default assumptions adds uncertainty to the exposure estimates.

EPA officials said that EPA did not use more current dietary intake data from USDA in the October 2001 draft reassessment because EPA has not yet fully reviewed surveys subsequent to the 1989-91 surveys that it uses in its *Exposure Factors Handbook*. EPA officials told us that they did not believe it was necessary to use more current data because the dietary habits of Americans have changed very little over the course of the past decade. These officials cited data collected in surveys conducted between 1994 and 1996 that show little change in the intake of the 10 foods compared with surveys conducted between 1989 and 1991.

EPA's and WHO's Specific Reassessment Objectives and Processes Differed, but Their Analytical Methods and Conclusions on Dioxins' Health Risks Are Similar

EPA and WHO have undertaken extensive efforts to reassess the health risks of exposure to dioxins. EPA's comprehensive dioxin reassessment objective has been to characterize the potential human health risks posed by exposure to dioxins. To do this, EPA used an extensive, multiyear review process. In contrast, WHO had more narrowly focused primary objectives and conducted its reassessments of dioxins through a succession of individual reviews and meetings. Nonetheless, EPA and WHO used very similar analytical methods to identify the types of potential human health hazards associated with exposure to dioxins and assess the probability and severity of harm given different levels of exposure. Moreover, the conclusions EPA and WHO reached on the basis of their respective reassessments also reflected much agreement. However, there were some significant issues on which EPA and WHO differed, such as whether there are threshold doses of dioxins to which humans could be exposed over a lifetime without significant risk of cancer and whether dioxins other than TCDD are human carcinogens.

EPA Undertook a Comprehensive Assessment, While WHO Used a Succession of Individual Reviews and Meetings

In general, both EPA and WHO focused their evaluations of the health effects and risks associated with dioxins on TCDD and 28 other related chemical compounds (including 12 dioxin-like PCBs) for which consensus toxic equivalency factors had been established through a 1997 meeting organized by WHO.[20] However, there were important differences in some of the specific objectives of EPA's and WHO's dioxin reassessments and the processes used by EPA and WHO to develop the reassessments.

EPA's overall objective has been very broad: to characterize the available scientific information on the potential health risks posed by exposures to dioxins. EPA therefore addressed each of the four major components of a chemical risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization.[21] The resulting characterization of risks posed by dioxins can be used to inform risk management decisions, such as whether and where to set or revise regulatory standards, but other information and factors would also enter into such decisions.[22] The process by which EPA has undertaken this task has been a comprehensive, multiyear review. Moreover, the EPA reassessment has included multiple independent scientific peer reviews of various draft reports by EPA's Science Advisory Board and others. EPA has also solicited public review and comments on its draft reassessment.

WHO's reassessment objective also addressed a broad range of data and issues regarding the potential exposures and health risks associated with dioxins, but the specific reports and evaluations WHO produced on dioxins generally had more narrowly focused primary objectives than EPA's reassessment report. In addition, rather than a comprehensive,

[20]Because the results of this expert meeting were not published until 1998, EPA refers to this international consensus scheme as the TEQ-WHO_{98} update. See Martin Van den Berg, et al., "Toxic Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for Humans and Wildlife," *Environmental Health Perspectives* (1998): Vol. 106, No. 12: 775-792.)

[21]See U.S. General Accounting Office, *Chemical Risk Assessment: Selected Federal Agencies' Procedures, Assumptions, and Policies*, GAO-01-810 (Washington, D.C.: Aug. 6, 2001) for a more detailed description of the four-step process and other chemical risk assessment procedures that may be used by EPA.

[22]See U.S. General Accounting Office, *Environmental Protection Agency: Use of Precautionary Assumptions in Health Risk Assessments and Benefits Estimates*, GAO-01-55 (Washington, D.C.: Oct. 16, 2000) and GAO-01-810.

integrated process such as EPA's, WHO's process consisted of individual evaluations and meetings for each of those particular objectives.[23]

- In 1997, the International Agency for Research on Cancer (IARC), a chief contributor to WHO's dioxin risk assessments, published monographs covering TCDD and 16 other dioxins. (This agency publishes the results of its evaluations of specific chemicals in its series IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. In the rest of this report, we call the monographs covering TCDD and other dioxins the 1997 cancer monographs.) The primary objective leading to these monographs was to classify TCDD and other specific dioxins under a standard scheme that identifies whether and under what circumstances substances are human carcinogens.[24] Essentially, this objective corresponds to the hazard identification step of EPA's four-step risk assessment process.
- Under its activities related to the European Centre for Environment and Health, WHO organized two meetings of experts addressing issues on the health effects of dioxins. In June 1997, WHO convened experts in Stockholm, Sweden, to derive consensus toxic equivalency factors for 29 dioxins that could be used for human, fish, and wildlife risk assessments. In May 1998, WHO convened 40 experts from 15 countries in Geneva, Switzerland, to evaluate scientific data on the health risks and exposures of dioxins with the principal objective of updating the estimated amount of dioxins to which humans can be exposed daily without appreciable harm. In the rest of this report, we call these efforts, respectively, the 1997 TEF meeting and the 1998 consultation.
- At the 57th meeting of the Food and Agriculture Organization of the United Nations/WHO Joint Expert Committee on Food Additives in June 2001 in Rome, Italy, the committee for the first time evaluated the risks associated with the presence of dioxins in food. The participants specifically evaluated dioxins (among other specific food additives and contaminants), with the view toward recommending acceptable intakes for dioxins contained in foods. The committee used the 1998 consultation's assessment as the starting point for its evaluation but took

[23]EPA experts participated in all of these international meetings and evaluations convened by WHO on dioxins.

[24]Group 1 is the classification for chemical agents or mixtures that WHO's reviewers determine are carcinogenic to humans. Group 2A is the classification for those probably carcinogenic, and Group 2B for those possibly carcinogenic. Group 3 includes those not classifiable as to human carcinogenicity, and Group 4 covers those probably not carcinogenic.

into account newer studies. In the rest of this report, we call this evaluation the 2001 food additives meeting.

Appendix I highlights some of the major milestones in the EPA and WHO assessments of dioxin risks, with a particular focus on the reassessment efforts that both entities began in the 1990s.

EPA and WHO Used Similar Analytical Methods

Despite differences in some of the specific objectives and processes of their respective reassessment efforts, EPA and WHO used similar analytical methods to identify and assess the potential health risks of dioxins. Through these analyses, EPA and WHO identified the types of potential hazards that might be associated with exposure to dioxins, the circumstances under which these substances could cause adverse effects, and the probability and severity of expected effects given different levels of exposure to dioxins. Specifically, both EPA and WHO

- reviewed available scientific data from many studies of humans and animals covering a variety of effects potentially associated with exposure to dioxins;
- continued to consider cancer risks, as in the original dioxin risk assessments, but also paid increasing attention to noncancer health effects, such as changes in reproductive and developmental functions and the immune and nervous systems, as well as other health problems, such as chloracne (a chronic and disfiguring skin disease) and alterations in liver enzyme levels;
- reviewed evidence regarding other biochemical, molecular, or cellular effects that have been observed in various studies, agreeing that these effects might be precursors to subsequent adverse effects; and
- considered a range of analytical methods, models, and approaches to assess the dose-response relationships for exposure to dioxins.

EPA and WHO also used some analytical concepts and methods that they agreed were more appropriate to the analysis of dioxins than those that are often used for risk assessments of other chemicals. For example, both entities used body burden—the concentration of dioxins in the body—instead of other dose measures, such as daily intake, to compare risks between humans and animals and determine doses that would be of equivalent risk in humans and animals. The organizations also concurred that the concept of toxic equivalency should be used to facilitate risk assessment of dioxins and complex mixtures of dioxins. Furthermore, in contrast to chemical risk assessments in general, EPA and WHO often had sufficient data to focus on the dose level associated with a 1-percent

increase in a particular effect (rather than being limited to the level associated with a 10-percent increase) and seldom had to extrapolate outside the observed doses or exposures from the studies that they used to prepare the reassessments.

Much of the scientific data available to EPA and WHO on the potential effects of exposure to dioxins came from animal studies, mainly studies of TCDD on a variety of species. (According to WHO, most other dioxins and dioxin-like compounds are "relatively poorly studied" compared with TCDD.[25]) However, EPA's and WHO's recent reassessment efforts also benefited from the increasing quantity and quality of data on the effects of dioxins in humans that became available during their reassessments. Among the sources of these human data were studies of occupational exposure of people who produce and apply herbicides; residents in a contaminated area of Seveso, Italy (where an accident at a chemical factory had released a cloud of toxic chemicals, including dioxins, in 1976); and noncancer effects in infants and children.

EPA and WHO Had Similar Overall Conclusions but Differed on Some Important Issues

The conclusions EPA and WHO reached on the basis of their respective dioxin reassessments were frequently similar, but some significant differences also emerged. With respect to the major areas of agreement, both EPA and WHO concluded that TCDD is a human carcinogen and that

- dioxins can cause a variety of both cancer and noncancer health effects,
- dioxins act in the same way within the body to cause the effects observed in animals and humans,
- dioxins adversely affect human health at lower exposure levels than previously thought, and
- some effects could occur at or near the levels to which the general population is now being exposed.

EPA and WHO not only concurred at the broad level of these conclusions but also on many of the supporting details. For example, both entities had similar reasons for concluding that TCDD is a human carcinogen: the combination of sufficient evidence that TCDD causes cancer in animals,

[25]EPA's reassessment also noted that there is a broad range in the quality and quantity of data available for individual dioxins. However, EPA pointed out that five dioxins (including TCDD) contribute approximately 80 percent of the total toxic equivalence of dioxin in humans and characterized these five chemicals as "well studied." Nevertheless, EPA's reassessment relied primarily on TCDD studies.

more limited evidence of carcinogenicity from human data, and strong evidence that TCDD operates through the same mode, or mechanism, of action in animals and humans.[26]

The major differences of opinion between EPA and WHO concerned whether (1) there is a threshold below which exposure to dioxins would not be expected to cause cancer, (2) it is useful to calculate a "tolerable" dose of dioxins or estimate a dose without appreciable risk of deleterious effects to which humans can be exposed over a lifetime, and (3) both mixtures of dioxins and dioxins other than TCDD are likely human carcinogens. In addition, EPA quantified the general population's possible additional risk of developing cancer from exposure to dioxins, while WHO did not. Such differences may make it more difficult for interested parties to compare the results of EPA and WHO dioxin risk assessments. The following sections provide additional information on each of these differences.

Cancer Threshold

EPA and WHO disagreed about whether there is a threshold below which exposure to dioxins would not cause cancer. EPA concluded that available evidence was insufficient for the agency to depart from its default linear cancer risk assessment approach, which is based on an assumption that no threshold exists regarding adverse effects (i.e., any exposure to carcinogenic substances, no matter how small, poses some risk of developing cancer).[27] In contrast, WHO concluded that there is a threshold for all adverse effects, including cancer. Specifically, WHO concluded that dioxins do not initiate cancer through a direct effect on genetic material (that is, they are non-genotoxic carcinogens) and, therefore, do not warrant a linear (no threshold) assessment of risk. WHO also concluded that noncancer health effects occurred at lower body burdens (concentrations) of dioxins than the body burdens at which cancer occurred in animals. Accordingly, WHO determined that establishing a tolerable intake based on estimated thresholds for noncancer effects would also address any cancer risks (that is, if the intake were set to avoid

[26]The National Toxicology Program of the Department of Health and Human Services also listed TCDD as a known human carcinogen in the 2001 addendum to its *Report on Carcinogens* (9th edition) on the basis of a similar combination of epidemiological (human) and mechanistic information, supported by experimental animal studies.

[27]EPA's risk assessment guidelines set forth "default" assumptions—generic approaches based on general scientific knowledge and policy judgment that are applied to various elements of the risk assessment process when specific scientific information is not available.

appreciable noncancer health consequences, it should also avoid appreciable consequences concerning cancer).

Estimating a "Tolerable" Dose or One Without Appreciable Risk

WHO programs estimated a tolerable daily intake for dioxins in 1998 and a tolerable monthly intake in 2001. These measures represent the amounts of dioxins that the WHO experts believe a human could ingest daily or monthly for a lifetime without appreciable health consequences. Expressing these estimates as "tolerable" intakes generally does not connote that such intakes are acceptable or risk free, but rather that any health consequences would be judged to be tolerable while exposure is continuing to be reduced.[28] EPA's related (but not identical) measure is the reference dose, which would estimate a daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects during a lifetime.[29] EPA, however, chose not to calculate a reference dose for dioxins, as it generally does for noncancer health assessments of other substances. According to EPA, it did not do so because any reference dose that it would recommend for dioxins would likely be below (perhaps considerably below) the current background intake levels and body burdens of the U.S. population. EPA pointed out that reference doses are typically calculated to address the risks of incremental exposures over background exposure.[30] In the case of dioxins, however, background exposure is a significant component of total exposure. Therefore, in EPA's opinion, a reference dose would be uninformative to risk managers for safety assessment. EPA also noted that, if it were to set a reference dose, its estimate likely would be more

[28]Although the experts participating in WHO's 1998 consultation established a tolerable daily intake range of 1 to 4 picograms per kilogram of body weight, they also stressed that the ultimate goal should be to reduce human intake levels below that range and recommended that every effort should be made to reduce exposure to the lowest possible level.

[29]The Agency for Toxic Substances and Disease Registry in the Department of Health and Human Services uses a similar measure known as the minimal risk level. Minimal risk levels are estimates of the daily human exposure to a hazardous substance that are likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. These substance-specific estimates are intended to serve as screening levels to identify contaminants and potential health effects that may be of concern at hazardous waste sites. In 1999, the Agency for Toxic Substances and Disease Registry set a minimal risk level for dioxins and related compounds of 1.0 picogram TEQ per kilogram of body weight per day, but did not use body burden as a dose metric.

[30]Background exposure to chemicals is the exposure that regularly occurs to members of the general population from media such as food, air, and soil that have concentrations of these chemicals within normal background range.

stringent than the tolerable intake levels for dioxins proposed by WHO because EPA's traditional approach for setting a reference dose gives more weight to scientific uncertainties than the approach WHO used in setting its tolerable intake level.

EPA chose instead to use an alternative approach, the margin of exposure, to characterize noncancer risks. The margin of exposure is a ratio that shows how far the actual (or estimated) total human exposure to a particular substance is from levels at which adverse effects have been demonstrated to occur in human or animal studies. The margin of exposure is an alternative way of characterizing the likelihood that noncancer effects may be occurring in the human population at environmental exposure levels. A reference dose, on the other hand, estimates a level of exposure below which EPA considers it unlikely that any adverse effects will occur. EPA generally considers margins of exposure of 100 or more as adequate to rule out the likelihood of significant effects occurring in humans. However, for the most sensitive effects identified with dioxins (i.e., those that occurred at the lowest doses of exposure), the margins of exposure ranged from 15 to less than 1.

Characterizing Cancer Risks Posed by TCDD, Other Individual Dioxins, and Mixtures of Dioxins

EPA and WHO both characterize TCDD as carcinogenic to humans. While EPA further characterizes other individual dioxins and mixtures of dioxins as "likely to be human carcinogens," WHO does not. Specifically, WHO states that the carcinogenicity of dioxins other than TCDD cannot be determined because of insufficient data. This difference of opinion largely reflects the specific objectives and scopes of EPA's and WHO's assessments. EPA's conclusion reflects a "weight of the evidence" judgment—that is, it is based on EPA's entire reassessment of dioxins (resting, in particular, on the conclusion that all dioxins share a similar mode of action and using evidence from both animal and human studies). In contrast, WHO's cancer monographs looked only at individual dioxins, focusing on whether they met specific criteria. Consequently, WHO's conclusions reflected a narrower data set and did not address the risks posed by mixtures of dioxins. However, because most human exposure is to mixtures rather than individual dioxins, and both EPA and WHO advocate using the same toxic equivalency factors for assessing the dioxins in such mixtures, any differences in the carcinogenicity classifications may have little practical impact.

Quantifying Cancer Risks

Quantifying the lifetime cancer risk to the general population from exposure to dioxins was an important component of EPA's dioxin reassessment. EPA estimated that the upper bound on the general population's lifetime risk for all cancers from dioxins might be on the order of 1 in 1,000 or more (i.e., people might experience a 1 in 1,000 increased chance of developing cancer over their lifetime because of exposure to dioxins). EPA's reassessment also states that the vast majority of the population is expected to have less risk per unit of exposure and some may have zero risk. WHO did not carry out such a quantitative assessment of the general population's cancer risk for two main reasons. First, calculations of population risk are beyond the scope of WHO's IARC cancer monographs, which evaluate whether and under what circumstances particular substances could pose a cancer risk to humans but generally do not provide quantitative risk estimates.[31] Second, as noted previously, WHO's conclusion about a cancer threshold for dioxins led it to focus on noncancer effects when deriving tolerable intake levels for dioxins. However, WHO did explore the calculation, through modeling, of a cancer "benchmark dose," the dose or body burden estimated to result in a 1-percent increase in cancer mortality. But WHO noted that its estimates for this benchmark dose ranged quite widely and strongly depended on the assumptions made during the modeling.

Appendix II provides a more detailed comparison of the EPA and WHO conclusions regarding a number of major issues covered by the entities' dioxin risk assessments.

[31]WHO's IARC working groups may do some quantitative evaluations of human data in the monographs, but without extrapolation beyond the range of data available. Quantitative extrapolation of cancer risks from experimental (animal) data to the human situation is not undertaken.

EPA's Draft Dioxin Reassessment Report Generally Reflects the Views of Recent Peer Reviews

Two independent peer review panels, including an EPA Science Advisory Board[32] panel, reviewed major sections of EPA's draft dioxin reassessment report in 2000. Both panels generally agreed with a number of key assumptions and approaches that EPA used to develop its updated health risk assessment of dioxins. Each of the peer review panels had a number of recommendations and suggestions for EPA to address or consider, most of which focused on the approaches and methodologies used to depict the health risks associated with dioxins. EPA made a number of revisions to its draft report in response to these recommendations and comments. The peer review panels disagreed with EPA on a few major points, and the Science Advisory Board panel emphasized the need for additional research to bridge gaps in data.

Two Peer Review Panels Reviewed the Draft Dioxin Reassessment Report in 2000 and Concurred on Many Key Aspects

Both an independent expert peer review panel and one convened by EPA's Science Advisory Board reviewed the draft reassessment report on dioxins in 2000. These reviews resulted in part from the Board's review of an earlier version of EPA's draft reassessment report. In 1995, a Board panel had reviewed the draft reassessment and requested that EPA make substantive revisions to the chapter on dose-response modeling[33] and to the *Integrated Summary*. The Board had also requested that EPA develop a separate chapter on toxicity equivalence factors and submit the revised dose-response and new toxicity chapters to external peer review before the next Board review of these sections. In response, EPA revised the chapter on dose-response modeling and had it peer reviewed in 1997. Similarly, EPA wrote a chapter on toxicity equivalence factors and had it peer reviewed as part of the July 2000 review.

July 2000 External Peer Review Panel

In July 2000, EPA organized an independent peer review panel to review the revised *Integrated Summary* and the new chapter on toxicity equivalence factors. To obtain an objective critique, EPA had a contractor select 12 independent individuals with expertise in several technical fields, including risk characterization and communication; toxicology; epidemiology; sources of, and population exposure to, dioxins and related

[32]EPA's Science Advisory Board reviews key scientific studies and methodologies used by the agency in formulating rules to protect the environment and public health. The Board comprises nongovernment experts and provides technical advice directly to the EPA administrator primarily on the basis of its peer reviews—that is, critical evaluations by panels of independent experts.

[33]Dose-response modeling is used to estimate the health risks associated with various exposure levels (dose).

compounds; mechanisms and mode of action; and toxic equivalency. The panel addressed 20 questions about the reassessment report regarding exposure to and the health risks of dioxins. Table I of appendix III lists the questions the July 2000 panel addressed in its review.

The panel generally agreed with the approaches and methodologies EPA used in its reassessment, and noted, among other things, the following:

- Body burden—the concentration of dioxins in the body—is an appropriate "dose metric" (measure) for comparing health risks across species.
- The use of margin of exposure—a ratio that shows how far actual or estimated human exposure is from levels at which adverse effects have been demonstrated to occur in human or animal studies— is a more logical approach to characterizing noncancer risk of dioxins than comparing exposure to a reference dose.
- The report's information on noncancer effects in animals and humans was adequately assembled, and the explanation of why dioxins' effects observed in animals are of concern to humans was also sufficient.
- The history, rationale, and support for the toxicity equivalence approach, which is used to assess risks posed by dioxins and complex mixtures of dioxins on the basis of their toxicity relative to an equivalent dose of TCDD, were adequately presented.

As discussed further below, the July 2000 panel also provided several recommendations and suggestions and identified the topics of greatest concern for finalizing the *Integrated Summary*.

The Board Panel

Once the July 2000 panel published its recommendations and suggestions in August 2000, EPA addressed them and sent its revised draft to the Science Advisory Board's dioxin reassessment review subcommittee panel in September 2000. The panel comprised several professors and directors employed by medical institutions and representatives of industry-affiliated research organizations, consulting firms, and state health agencies. The Board panel met to review the revised sections of the draft reassessment report in November 2000. The Board agreed to answer 20 questions on the reassessment report regarding exposure to and the health risks of dioxins. Most of these questions were similar to those asked of the July 2000 panel. The Board panel completed its review and published a report in May 2001. Table 2 of appendix III lists the questions the Board panel addressed in its review.

The Board panel, as the July 2000 panel before it, endorsed several key aspects of the reassessment, noting that, among other things, EPA had

- used appropriate dose metrics, such as body burden, to equate risks across species;
- assembled and distilled a large and diverse body of literature on noncancer effects into a coherent document;
- properly chosen the margin-of-exposure approach to characterize noncancer risks;
- used toxicity equivalence factors to effectively address the joint effects of complex mixtures of dioxins on human health; and
- compiled an outstanding inventory of dioxin sources and effectively characterized the estimates of background exposure to dioxins using the available scientific data.

The Board panel stated that, overall, EPA had prepared a thorough and objective summarization of the data and had addressed the key issues the Board had set forth in its 1995 review of the draft. The Board panel concluded that there was no need to submit further revisions of the reassessment report and that EPA should proceed to complete and release the document. However, as discussed in the following section, the Board panel provided several recommendations and suggestions for EPA to improve the draft document before its release. The Board panel also recognized the need for additional research to bridge gaps in data that limit EPA's ability to determine the magnitude of the health risks associated with dioxins. In essence, the Board panel viewed this reassessment as an interim assessment, recognizing that the data gaps are not likely to be addressed in the foreseeable future.

EPA's Draft Reassessment Report Reflects Changes Made in Response to Recommendations and Suggestions of Peer Reviews

While the peer review panels generally agreed with the methodologies and approaches used by EPA, they made a number of recommendations and suggestions, and the Board asked specifically that the agency either address them before this reassessment is released in 2002 or in a future assessment of dioxins. The panels' recommendations generally reflected either a consensus of the panelists or the opinion of a majority. EPA generally addressed the panels' recommendations and suggestions by performing additional analyses, adding or revising text, identifying the recommendations or suggestions as related to EPA's long-term research goals, or indicating that the data currently available are not adequate to address the recommendation or suggestion. Additional changes are now being made as EPA prepares the draft for external interagency review.

Four of the five recommendations by the July 2000 panel regarded improvements EPA could make to the section on health risks associated with dioxins. The July 2000 panel recommended that EPA

- explicitly explain the relationship between body burden and daily intake, serum levels, and tissue dose;
- include a table in the final reassessment report summarizing the various noncancer effects observed in animals and humans at low-level exposures;
- improve the methodologies used in determining the cancer risks of dioxins—such as requesting more detail on exactly how the cancer slope factor[34] for estimating cancer risks of the general population was derived; and
- reexamine the basis for its estimate of the upper bound cancer risks to the general population.

The fifth recommendation of the July 2000 panel involved the use of specific terminology in the exposure section. In addition, this panel had several suggestions regarding the health risks associated with dioxins, including that EPA

- provide more detail in the *Integrated Summary* on the implications of using the margin-of-exposure approach rather than comparing exposure with reference doses;
- more clearly describe the significance of the upper bound cancer risks to the public; and
- add discussion of the uncertainties associated with using various dose metrics specifically for evaluating childhood risks.

Ten of the 13 recommendations made by the Board panel also focused on the need to improve the section on health risks associated with dioxin. These recommendations included that EPA

- calculate a reference dose to evaluate risk in addition to using the margin-of-exposure approach to provide information on the minimum dose that humans can receive without suffering harm,
- improve its margin-of-exposure approach by more clearly explaining its choice to use dose levels associated with a 1-percent increase in a

[34]A cancer slope factor is an upper bound estimate of the increased cancer risk from a lifetime of exposure to an agent, generally approximating or exceeding the 95 percent confidence limit. This estimate is generally reserved for use in the low-dose region of the dose-response relationship.

particular effect and also by calculating a dose level associated with the 10-percent increase more commonly used in chemical risk assessments, and

- provide better justification for using a specific dose metric and identify the important data gaps that could affect the results of those choices.

Three of 13 recommendations asked that EPA improve the section on exposure to dioxins by evaluating the sources that contribute most to dioxins in the food chain, discussing all "special population" exposure in more detail, and extending breast-feeding exposure scenarios beyond 1 year.

EPA made many additions and changes to the draft reassessment in response to the peer review reports by both panels. For example, in response to recommendations from both panels, EPA revised and added text in several places to better explain the variety of dose metrics available and why body burden is the best choice for assessing dioxins, while acknowledging that EPA will need to address data gaps on body burden in the future as further research is completed. Tables 1 and 2 in appendix IV highlight the actions EPA took to address both panels' recommendations, suggestions, and concerns.

EPA and Peer Reviewers Do Not Agree on a Few Scientific Issues, and Uncertainties Remain Because Data Are Lacking

Overall, the peer review panels agreed with EPA's approach to the reassessment, and EPA generally addressed the recommendations, suggestions, and concerns of the peer review panels. In a few cases, EPA disagreed with the panels' recommendations or suggestions. In these cases, the agency explained its position in the text and, in the case of the July 2000 panel, addressed it in a separate written document. For example, although the Board panel had recommended that EPA calculate a reference dose and add it to the text, EPA chose to continue to use only the margin-of-exposure approach and not calculate a reference dose. EPA stated in the revised draft report that a calculated reference dose would be lower than most people's daily exposure and added a more detailed explanation of why it chose to use the margin-of-exposure approach.

In addition to disagreeing with EPA on a few key scientific issues, the peer review panels could not agree among themselves in some cases on EPA's findings. In such cases, the panels refrained from making recommendations or suggestions to the agency. For example, members of both peer review panels did not reach consensus on the strength of evidence used by EPA to support the classification of TCDD as a human carcinogen and other dioxin compounds as likely human carcinogens.

EPA officials believe that the weight of scientific evidence on human and animal exposure supports classifying TCDD as a known human carcinogen, a view also held by WHO and the U.S. Department of Health and Human Services.

Although neither panel specifically recommended that EPA change its classification of TCDD as a human carcinogen to a lesser category, such as a likely human carcinogen, for various reasons most of the peer reviewers did not endorse EPA's classification. For example, while the July 2000 panel agreed that TCDD is clearly a potent carcinogen in many species of animals, most of the panel thought that human epidemiology studies were too limited, and the results not consistent enough, to serve as a basis for showing increased cancer mortality. As a result, the majority felt that the characterization of TCDD as a known human carcinogen was not justified. Similarly, the Board panel also noted limitations in the scientific data, questioning the epidemiological data that indicated dioxins are carcinogens in humans, as well as the data that supported similar modes of action occurring in both animals and humans. Almost one-half of the Board did not support classification of TCDD as a known human carcinogen for various reasons. Those who did support the classification believed that the results from studies of TCDD-exposed workers were persuasive and that the variety of studies from researchers in different countries provided limited but convincing evidence of TCDD's carcinogenicity in humans.

Observations

A decade in the making, EPA's draft reassessment report on dioxins was both improved and limited by the passage of time, particularly in estimating the daily dietary intake of dioxins by the typical American adult. That is, EPA was able to include new food studies in the reassessment as they became available. At the same time, however, these and earlier studies that EPA relied on became less current with the passage of time. Overall, while EPA's draft reassessment report has advanced the state of knowledge on dietary exposure to dioxins in the United States, the extent to which the estimate accurately reflects current average daily exposure is not known. EPA acknowledges the need for additional research on dietary intake, identifying a number of data limitations associated with the estimates it developed in its October 2001 draft report. Future efforts could eliminate most of the food data limitations of the reassessment. Such efforts could include periodic, comprehensive food surveys that analyze samples of the most commonly eaten food products in each type of food studied, with samples collected within the same time frames and analyses performed using standardized

methodologies. Further, when they become available, the results of the ongoing EPA/USDA follow-up study on dioxin levels in beef, pork, and poultry should provide quantitative information on the changes, if any, in dioxin levels in these foods from the mid-1990's to the present.

Agency Comments and Our Response

We provided EPA with a draft of this report for its review and comment and the draft segment comparing EPA's and WHO's assessments of dioxins to WHO. In commenting on the draft report, EPA's assistant administrator, Office of Research and Development, said that the report was well researched and written and provided a balanced treatment of the information. However, EPA believed that additional information on some of the data limitations discussed in the section on EPA's estimates of the dietary intake of dioxins would better enable readers to evaluate the impact of the data limitations. Where appropriate, we revised the report to reflect the views EPA presented in its comments. For example, we added information concerning the strength of the food concentration data used in estimating national mean levels of exposure to dioxins, the sampling of animal fat rather than meat and poultry products sold in grocery stores, and the likelihood that current dioxin levels in food have significantly declined since the mid-1990s. EPA's comments and our evaluation of them are provided in appendix V.

In commenting on the draft segment comparing EPA's and WHO's analyses, a senior advisor of health and environment, the Department of Protection of the Human Environment, World Health Organization, said the report was well written and accurate.

Scope and Methodology

To describe the types and extent of data EPA used to reassess human dietary exposure to dioxins in the United States, we reviewed the relevant portions of the October 2001 draft reassessment, the 1994 and 2000 drafts that were peer reviewed, and the initial 1985 health risk assessment. We also reviewed EPA documents and journal articles on the agency's national sampling of beef, pork, and poultry samples, and information about the other samples used for milk, eggs, fish, dairy products, and vegetable fats. We discussed the samples and methodology issues about them with EPA officials and contractor staff. We did not validate or verify EPA's estimates of dietary exposure to dioxins.

To compare EPA's objectives, processes, analytical methods, and conclusions with those of WHO, we analyzed EPA's October 2001 draft reassessment report and various WHO publications on its objectives,

analyses, and conclusions. We discussed the similarities and differences with EPA and WHO officials.

To determine the extent to which EPA's draft dioxin reassessment reflects the views of two independent peer review panels, we analyzed the recommendations, suggestions, and concerns in the reports by the EPA Science Advisory Board's dioxin reassessment review subcommittee panel—on reviews performed in 1994 and 2000—and a report from another independent peer review panel on its July 2000 review. Recommendations of the Board panel were noted in bold print in the executive summary, and we considered other statements to be "suggestions" when they were the consensus opinion of the panelists or the opinion of a majority or of some of the panelists. We considered the July 2000 panel's statements to be "recommendations," "suggestions," or "concerns," when those particular words were used in the executive summary and where the statements reflected either a consensus or the opinion of a majority or of some of the panelists. We also reviewed EPA documentation to determine the changes EPA has made to its draft reassessment as a result of being peer reviewed, including comparing the agency's previous drafts of the reassessment with each other and reviewing the written responses to the July 2000 panel's recommendations and suggestions. We also met with EPA officials to identify the agency's responses to the panels' recommendations, suggestions, and concerns, including discussing those with which it disagreed.

We conducted our work from July 2001 through March 2002 in accordance with generally accepted government auditing standards.

We will send copies of this report to the administrator, EPA, and make copies available to others who request them. This report will also be available on GAO's Web site (www.gao.gov).

If you or your staff have questions about this report, please call me on (202) 512-3841. Key contributors to this report are listed in appendix VI.

David G. Wood

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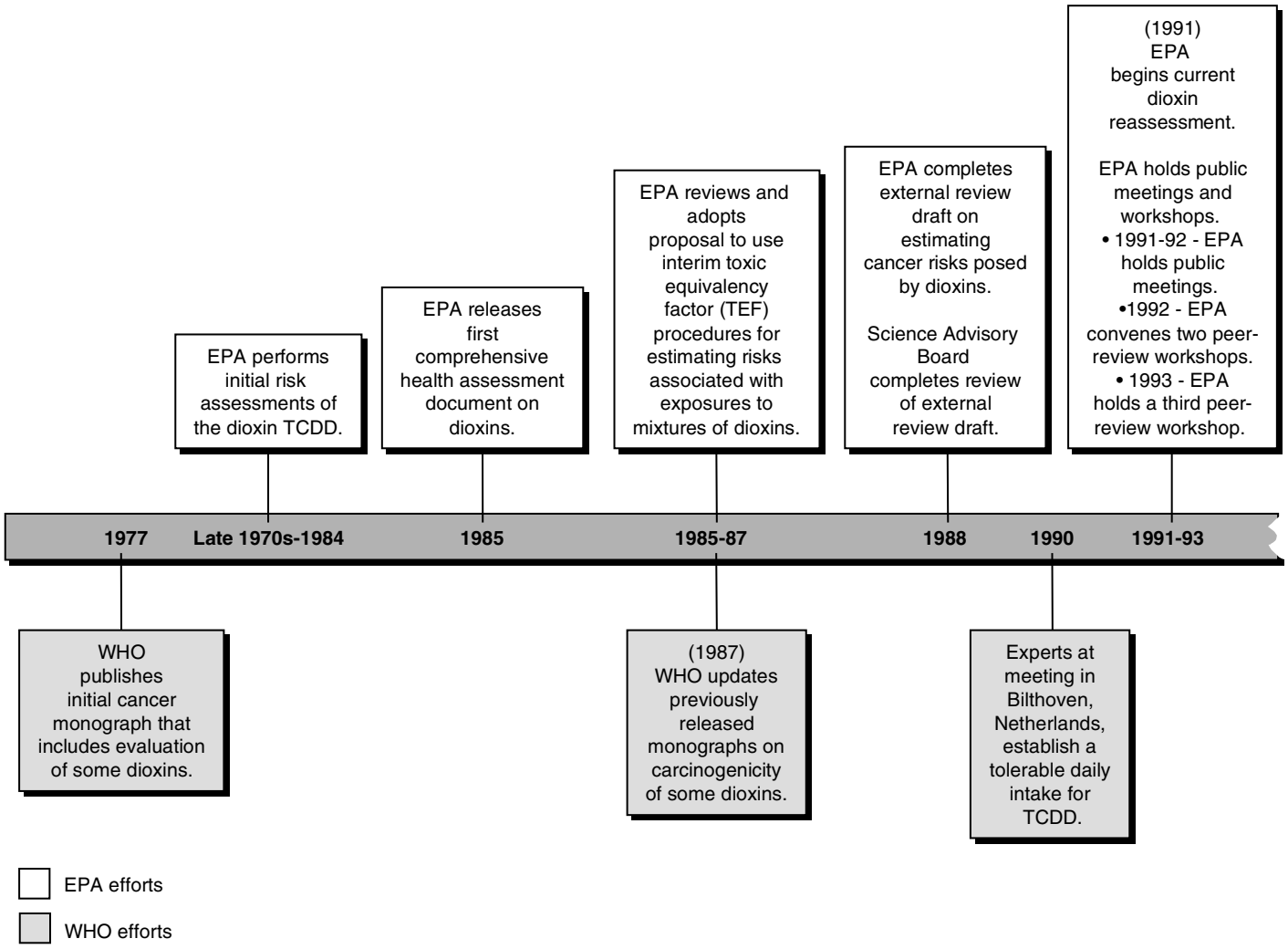
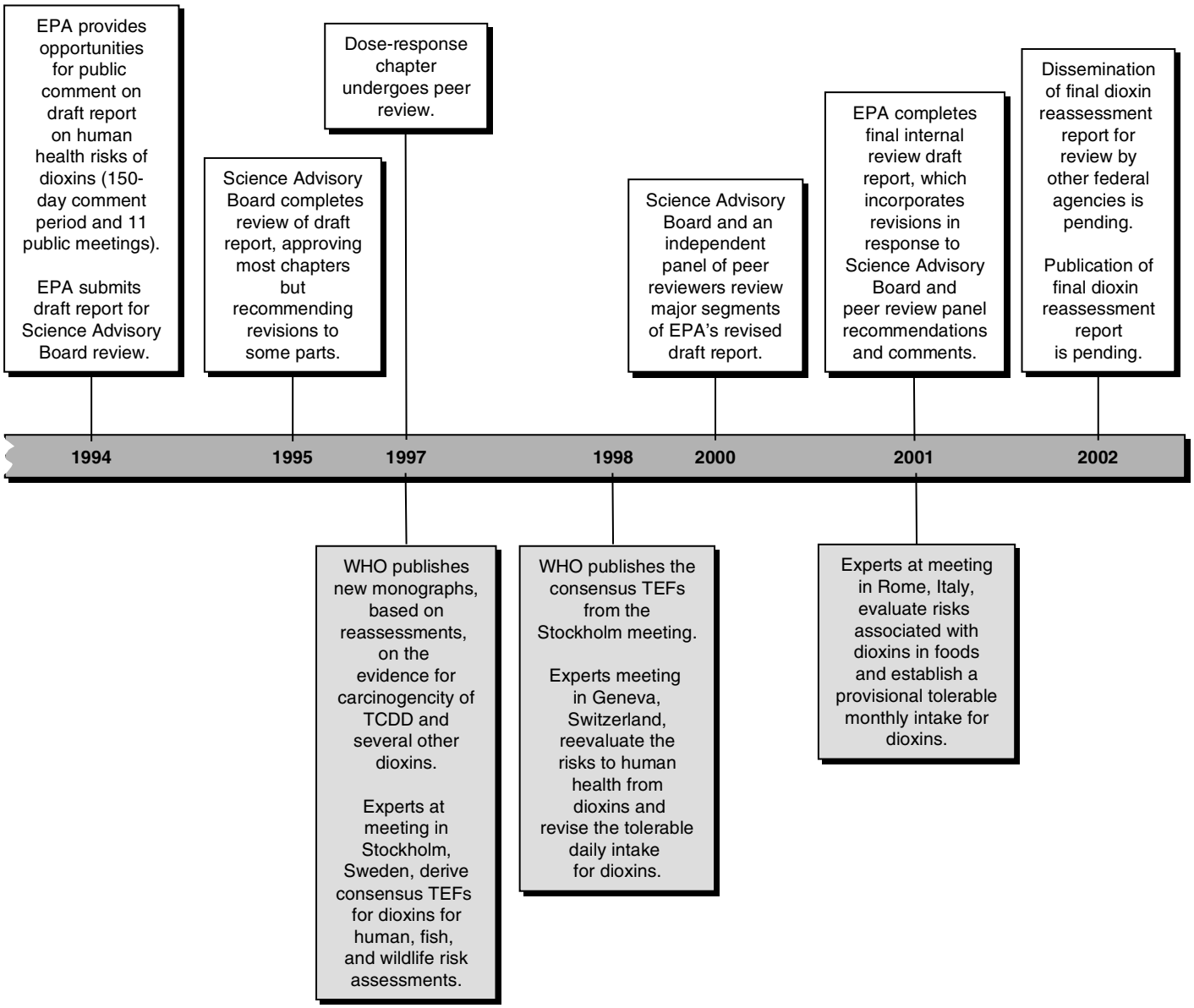
Appendix I: Major Milestones in the EPA and WHO Dioxin Risk Assessment Efforts




EPA provides opportunities for public comment on draft report on human health risks of dioxins (150-day comment period and 11 public meetings).
EPA submits draft report for Science Advisory Board review.
Science Advisory Board completes review of draft report, approving most chapters but recommending revisions to some parts.
Dose-response chapter undergoes peer review.
Science Advisory Board and an independent panel of peer reviewers review major segments of EPA's revised draft report.
EPA completes final internal review draft report, which incorporates revisions in response to Science Advisory Board and peer review panel recommendations and comments.
Dissemination of final dioxin reassessment report for review by other federal agencies is pending.
Publication of final dioxin reassessment report is pending.
1994
1995
1997
1998
2000
2001
2002
WHO publishes new monographs, based on reassessments, on the evidence for carcinogencity of TCDD and several other dioxins.
Experts at meeting in Stockholm, Sweden, derive consensus TEFs for dioxins for human, fish, and wildlife risk assessments.
WHO publishes the consensus TEFs from the Stockholm meeting.
Experts meeting in Geneva, Switzerland, reevaluate the risks to human health from dioxins and revise the tolerable daily intake for dioxins.
Experts at meeting in Rome, Italy, evaluate risks associated with dioxins in foods and establish a provisional tolerable monthly intake for dioxins.

Appendix II: Comparison of the Major Conclusions from EPA's and WHO's Dioxin Risk Assessments

EPA conclusions	WHO conclusions
Effects associated with exposure to dioxins	
Exposure to dioxins can produce a wide variety of effects in animals (including cancer and noncancer health effects) and might produce many of the same effects in humans. EPA characterizes dioxin and related compounds as carcinogenic and developmental, reproductive, immunological, and endocrinological hazards and makes the following specific points.[a] • Exposure to TCDD leads to an increased risk of generalized cancers at multiple organ sites, including lung cancer. • Long-term noncancer consequences of exposure to TCDD in adults include chloracne, elevated gamma glutamyl transferase levels, and altered testosterone levels.[b] Among the possible noncancer consequences of exposure to TCDD or other dioxin and dioxin-like compounds are dermatological conditions such as chloracne; liver diseases; and kidney, nervous system, and lung disorders. • Although available data suggest an association between TCDD exposure and other adverse outcomes, further study is required of circulatory and heart disease, diabetes and glucose metabolism, reproductive and developmental outcomes, and immunologic disorders.	Exposure to dioxins may be linked to a variety of adverse effects. • Short-term human exposure to high levels of dioxins may result in skin lesions (such as chloracne) and altered liver function. • Long-term exposure is linked to impairment of the immune system, the developing nervous system, the endocrine system, and reproductive functions. • Chronic animal exposure to dioxins has resulted in several types of cancer. Human data from occupational or accidental exposure has produced evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites.
Mode of action through which exposure to dioxins can lead to adverse effects	
Dioxins are structurally related and elicit their effects through a common mode of action—binding of dioxins to a cellular protein called the aryl hydrocarbon receptor. Binding to the aryl hydrocarbon receptor appears to be necessary for all well-studied effects of dioxins but is not sufficient, in and of itself, to elicit these responses. TCDD and related compounds have a common mode of action in animals and humans. Therefore, there is no reason to expect, in general, that humans would not be similarly affected as animals at some dose.	A broad variety of data has shown the importance of the aryl hydrocarbon receptor in mediating the biological effects of dioxins. The precise chain of molecular events by which the receptor elicits these effects is not yet fully understood. However, alterations in key biochemical and cellular functions are expected to form the basis for dioxin toxicity. Experimental data indicate that TCDD and probably other polychlorinated dibenzo-p-dioxins (CDD) and polychlorinated dibenzofurans (CDF) are not direct-acting genotoxic agents (i.e., do not directly affect genetic material). Dioxins act through the same mode of action in animals and humans.

EPA conclusions	WHO conclusions
Use of the toxicity equivalency (TEQ) concept	
EPA and the international scientific community have adopted TEQ of dioxins as prudent science policy. (EPA recommended that the TEFs derived by WHO in 1997—published in 1998—be used to assign TEQ to complex environmental mixtures for assessment and regulatory purposes.)	The complex nature of CDD, CDF, and polychlorinated biphenyls (PCB) mixtures complicates the risk evaluation for humans. The concept of TEFs has been developed to facilitate risk assessment and regulatory control of exposure to these mixtures. (WHO derived updated consensus TEFs for 29 dioxins in 1997, with the results of the meeting published in 1998. Subsequent WHO assessments of dioxins used this updated set of TEFs for their calculations.)
Whether dioxins are human carcinogens	
Complex mixtures of dioxins are highly potent, "likely" human carcinogens. • A weight-of-the-evidence evaluation suggests that mixtures of dioxins are strong cancer promoters and weak direct or indirect initiators and are likely to present a cancer hazard to humans.[c] • Because dioxins and related compounds always occur in the environment and in humans as complex mixtures of individual congeners, it is appropriate that the characterization apply to the mixture. Individual congeners can also be characterized as to their carcinogenic hazards. • TCDD is best characterized as "carcinogenic to humans." Based on the weight of all evidence (human, animal, and mode of action), TCDD meets the criteria that allow EPA and the scientific community to accept a causal relationship between TCDD exposure and cancer hazard. • Other individual dioxin-like compounds are characterized as "likely to be human carcinogens" primarily because of the lack of epidemiological evidence associated with their carcinogenicity, although the inference based on TEQ is strong that they would behave in humans as TCDD does. Other factors, such as the lack of compound-specific chronic animal studies, also support this characterization.	TCDD is a human carcinogen (group 1), considering limited evidence in humans, sufficient evidence in experimental animals, and evidence of a mode of action that functions the same way in humans as in experimental animals.[d] Other dioxins are not classifiable as to their carcinogenicity to humans (group 3). Depending on the specific compound evaluated, the International Agency for Research on Cancer (IARC) noted that the available data provided inadequate evidence for carcinogenicity in humans or limited evidence, inadequate evidence, or evidence suggesting lack of carcinogenicity in experimental animals.

EPA conclusions	WHO conclusions
Whether there appears to be a "threshold" or safe dose of dioxins that would not cause adverse effects	
The supposition of a response threshold for receptor-mediated effects (such as those associated with dioxins' binding to the aryl hydrocarbon receptor) is a subject for scientific debate. The same receptor occupancy assumption of the classic receptor theory is interpreted by different parties as support for and against the existence of a threshold. Empirical dose-response data from cancer studies do not provide consistent or compelling support for threshold models and are insufficient to move from EPA's default policy of linear extrapolation (an approach that assumes there is no threshold of exposure without risk). Threshold levels of lifetime exposure to dioxins that would cause toxic noncancer effects may be below the current level of background exposure and body burdens, and, therefore, the potential exists for noncancer risk at background exposure.	TCDD does not affect genetic material, and there is a level of exposure below which cancer risk would be negligible. Although TCDD is classified by IARC as a human carcinogen, it is not considered to be a direct acting carcinogen. Therefore, a threshold approach could be used in the hazard assessment approach. A tolerable intake can be established for TCDD on the basis of the assumption that there is a threshold for all effects, including cancer. Because cancer occurred in animals at higher body burdens than other toxic effects, establishing a tolerable intake on the basis of noncancer effects would also address any carcinogenic risk.
Whether it is useful to set a dose or exposure level that the public could experience for a lifetime without expectation of harm	
EPA did not calculate reference dose or reference concentration values in this reassessment as it generally does for noncancer effects in other assessments. Instead, EPA chose to characterize the margins of exposure between estimated actual human exposure and the exposure levels at which studies indicated various adverse noncancer effects could occur.	The WHO 1998 consultation set daily limits on exposure levels of dioxins for non-cancer effects, a tolerable daily intake. The Joint Expert Committee on Food Additives of the United Nation's Food and Agriculture Organization and WHO set a provisional tolerable monthly intake limit on exposure levels to dioxins, again focusing on noncancer effects. The Committee participants felt that it was more appropriate to express the tolerable intake on a monthly rather than a daily basis because of the long half-life of dioxins (i.e., the body's stored dioxins decline slowly, with only half of the accumulated dioxins disappearing over about 7 years).

EPA conclusions	WHO conclusions
Human exposure to dioxins	
Human exposure to dioxins has occurred through background exposure, contamination of foods, occupational exposure, and exposure associated with industrial accidents. An increased background exposure can result from either a diet that favors consumption of foods high in dioxin content or a diet that is disproportionately high overall in animal fats. Most (more than 95 percent) background exposure results from the presence of minute amounts of dioxins in dietary fat, primarily from the commercial food supply. The average dioxin tissue level for the general U.S. adult population appears to be declining. Five compounds account for most (about 80 percent) of the toxicity in human tissue concentrations.	Human exposure to dioxins may occur through background (environmental) exposure and accidental and occupational contamination. Over 90 percent of human background exposure is estimated to occur through the diet, with food from animal origin being the predominant source. Recent studies show decreasing levels of dioxins in food and consequently a significantly lower dietary intake of these compounds.
Risks of adverse health effects at the general public's current levels of exposure to dioxins	
In general, EPA's assessments indicated that dioxins pose risks at lower levels of exposure than previously estimated and that the general public's current levels of exposure are at or near those that have been observed to cause harm. EPA estimates that the upper bound cancer risk at average current background body burdens exceeds 10^{-3} (i.e., the upper bound on general population lifetime risk for all cancers might be on the order of 1 in 1,000 or more). However, this is an upper bound estimate, so the true risks are likely less than that and may be zero for most people. • In 1985, EPA's estimate of the cancer slope factor based on exposure to TCDD was 1.6×10^{-4} per picogram of TCDD per kilogram of body weight per day (pgTCDD/kgBW/day).[e] • EPA's current upper bound slope factor for estimating human cancer risk on the basis of human data is 1×10^{-3} per pgTCDD/kgBW/day. • EPA's current upper bound slope factor for estimating human cancer risk on the basis of animal data is 1.4×10^{-3} per pgTCDD/kgBW/day. EPA estimated that U.S. residents are exposed daily to about 1 picogram of dioxins per kilogram of body weight, which is close to the level that caused biological changes in animals. EPA noted that the margins of exposure between estimated actual human exposure and the exposure levels at which studies indicated adverse noncancer health effects could occur were "considerably less than typically seen for environmental contaminants of toxicologic concern."	In general, WHO's assessments also indicated that dioxins pose risks at lower levels of exposure than previously estimated and that the general public's current levels of exposure are at or near those that have been observed to cause harm. In 1990, WHO experts had established a tolerable daily intake for TCDD of 10 picograms per kilogram of body weight. In 1998, the WHO consultation established a tolerable daily intake for dioxins at a range of 1-4 TEQ picograms per kilogram of body weight and noted that subtle effects may already occur in the general population at current background levels of 2 to 6 picograms per kilogram of body weight. The consultation stressed that the ultimate goal is to reduce human intake levels below 1 picogram TEQ per kilogram of body weight per day. In 2001, Joint Expert Committee on Food Additives of the United Nation's Food and Agriculture Organization of the United Nations and WHO determined that a monthly tolerable intake level made more sense than a daily level and established a provisional tolerable monthly intake of 70 picograms per kilogram of body weight per month (equivalent to 2.33 picograms per day) for dioxins. The various WHO entities did not calculate quantitative cancer risk estimates for the additional cancer risk that dioxins might pose to the general population. However, WHO did explore the calculation of a cancer "benchmark dose" (the dose or body burden estimated to result in a 1-percent increase in cancer mortality) through various models. On the basis of data from three industrial exposure studies, WHO estimated that the body

EPA conclusions	WHO conclusions
	burden of dioxins associated with a 1-percent excess cancer risk over a lifetime was 3 to 13 nanograms per kilogram of body weight, which is associated with a daily dose of dioxins in the range of 2 to 7 picograms per kilogram of body weight per day.
Risks to population subgroups	
Children's risks from dioxins and related compounds may be greater than that of adults, but more data are needed to fully address the issue. There may be individuals in the population who might experience a higher cancer risk on the basis of genetic factors or other determinants of cancer risk not accounted for in epidemiologic data or animal studies. In particular, a very small percentage of the population (less than 1 percent) may experience risks that are 2 to 3 times higher than the general population estimate if their individual response is at the upper bound and they are among the most highly exposed based on dietary intake of dioxins.	Certain population subgroups are at greater risk from dioxins. Fetuses are most sensitive to dioxin exposure, and newborns may also be more vulnerable to certain effects. Some individuals or groups of individuals may be exposed to higher levels of dioxins because of their diets or occupations.

[a]Endocrinological hazards are those related to the system of ductless glands that secrete hormones directly into the blood stream for distribution throughout the body, such as the pituitary, thyroid, and adrenal glands.

[b]Elevated gamma glutamyl transferase levels are among the changes in liver function and structure that have been observed using human data.

[c]According to EPA's revised proposed guidelines for carcinogen risk assessment, the descriptor "likely to be a human carcinogen" is appropriate when the available tumor effects and other key data are adequate to demonstrate carcinogenic potential to humans, yet not sufficient to infer a cause and effect relationship.

[d]For additional information on WHO-International Agency for Research on Cancer's (IARC) evaluation categories and the definitions of degrees of evidence, see the *Preamble to the IARC Monographs* available on the IARC Internet site (http://www.iarc.fr/).

[e]The cancer slope factor is an upper bound of the probability of cancer risk in the population. According to EPA, the slope factor generally approximates or exceeds a 95-percent confidence limit, meaning that there is a greater than 95-percent chance that cancer risks will be less than the upper bound.

Source: GAO review of EPA and WHO documents on dioxin reassessment efforts.

Appendix III: Questions EPA Asked Peer Review Panels to Address

EPA sought expert opinions from both a July 2000 panel of independent peer reviewers and a November 2000 Science Advisory Board expert panel on several key questions that pertain to the content of the documents under review. The questions are classified into 11 general topics. Most of the questions are the same for both panels. However, according to usual Science Advisory Board practice, EPA staff, Board staff, and the chair of the Board's dioxin reassessment review subcommittee jointly developed additional questions for the Board's review. Table 6 and table 7 show the topics and questions addressed by the July 2000 panel, and Board panel, respectively.

Table 6: Questions for the July 2000 Panel Review of EPA's Draft Dioxin Reassessment

Topic	Question
Body burden	1. Did EPA adequately justify its use of body burden as a dose metric for inter-species scaling? Should the document present conclusions based on daily dose?
Use of margin-of-exposure approach	2. How might the rationale be improved for EPA's decision not to calculate a reference dose/reference concentration, and for the recommended margin-of-exposure approach for conveying risk information? Is a margin-of-exposure approach appropriate, as compared to the traditional reference dose/reference concentration? Should the document present a reference dose/reference concentration?
	3. Are the calculations of a range of effective dose (ED)[01] body burden for noncancer effects in rodents responsive and clearly presented? Please comment on the weight of evidence interpretation of the body burden data associated with a 1 percent response rate for noncancer effects that is presented in Chapter 8, appendix I and figure 8-1 (where EPA considers that the data best support a range estimate for ED[01] body burdens from 10nh/kg to 50 ng/kg).
Mechanisms and mode of action	4. How might the discussion of mode of action of dioxin and related compounds be improved?
	5. Despite the lack of congener-specific data, does the discussion in the Integrated Summary and Risk Characterization support EPA's inference that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence?
TEFs	6. Is the history, rationale, and support for the TEQ concept, including its limitations and caveats, laid out by EPA in a clear and balanced way in Chapter 9? Did EPA clearly describe its rationale for recommending adoption of the 1998 WHO TEFs?
	7. Does EPA establish clear procedures for using, calculating, and interpreting toxicity equivalence factors?
Noncancer effects	8. Have the available human data been adequately integrated with animal information in evaluating likely effect levels for the noncancer endpoints discussed in the reassessment?
	9. Do reviewers agree with the characterization of human developmental, reproductive, immunological, and endocrinological hazard? What, if any, additional assumptions and uncertainties should EPA embody in these characterizations to make them more explicit?
Cancer effects	10. Do you agree with the characterization in this document that dioxin and related compounds are carcinogenic hazards for humans?
	11. Does the document clearly present the evolving approaches to estimating cancer risk (e.g. margin of exposure and the lower limit on ED[01] as a point of departure) as described in EPA's April 1996 "Proposed Guidelines for Carcinogenic Risk Assessment"? Is this approach equally as valid for dioxin-like compounds?

Topic	Question
	12. Please comment on the presentation of the range of upper bound risks for the general population based on this reassessment. What alternative approaches should be explored to better characterize quantitative aspects of potential cancer risk? Is the range that is given sufficient, or should more weight be given to specific data sources?
Background and population exposures	13. Have the estimates of background exposures been clearly and reasonably characterized?
	14. Has the relationship between estimating exposure from dietary intake and estimating exposure from body burden been clearly explained and adequately supported?
	15. Have important "special populations" and age-specific exposures been identified and appropriately characterized?
Children's risk	16. Is the characterization of increased or decreased childhood sensitivity to possible cancer and noncancer outcomes scientifically supported and reasonable? Is the weight-of-evidence approach appropriate?
Relative risks of breast feeding	17. Has EPA adequately characterized how nursing affects short-term and long-term body burdens of dioxins and related compounds?
Risk characterization summary statement	18. Does the summary and analysis support the conclusion that enzyme induction, changes in hormone levels, and indicators of altered cellular function seen in humans and laboratory animals represent effects of unknown clinical significance, but they may be early indicators of toxic response?
	19. Has the short summary statement in the risk and hazard characterization on page 107 adequately captured the important conclusions and the areas where further evaluation is needed? What additional points should be made in this short statement?
Sources	20. Are these sources adequately described and are the relationships to exposure adequately explained?

Source: EPA.

Table 7: Questions for the November 2000 Science Advisory Board Panel

Topic	Question
Body burden	1. Did EPA adequately justify its use of body burden as a dose metric for inter-species scaling? Should the document present conclusions based on daily dose?
Use of margin-of-exposure approach	2. Has EPA's choice of the margin-of-exposure approach to risk assessment adequately considered that background levels of dioxins have dropped dramatically over the past decade and are continuing to decline? How might the rationale be improved for EPA's decision not to calculate a reference dose/reference concentration, and for the recommended margin-of-exposure approach for conveying risk information? Is a margin-of-exposure approach appropriate, as compared to the traditional reference dose/reference concentration? Should the document present a reference dose/reference concentration?
	3. Are the calculations of a range of ED^{01} body burden for noncancer effects in rodents responsive and clearly presented? Please comment on the weight-of-evidence interpretation of the body burden data associated with a 1-percent response rate for noncancer effects that is presented in chapter 8, appendix I and Figure 8-1 (where EPA considers that the data best support a range estimate for ED^{01} body burdens from 10nh/kg to 50 ng/kg).

Topic	Question
Mechanisms and mode of action	4. How might the discussion of mode of action of dioxin and related compounds be improved?
	5. Despite the lack of congener-specific data, does the discussion in the Integrated Summary and Risk Characterization support EPA's inference that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence?
TEFs	6. Is the history, rationale, and support for the TEQ concept, including its limitations and caveats, laid out by EPA in a clear and balanced way in Chapter 9? Did EPA clearly describe its rationale for recommending adoption of the 1998 WHO TEFs?
	7. Does EPA establish clear procedures for using, calculating, and interpreting toxicity equivalence factors?
Noncancer effects	8. Have the available human data been adequately integrated with animal information in evaluating likely effect levels for the noncancer endpoints discussed in the reassessment? Has EPA appropriately defined noncancer adverse effects and the body burdens associated with them? Has EPA appropriately reviewed, characterized, and incorporated the recent epidemiological evidence for noncancer risk assessment for human population?
	9. Do reviewers agree with the characterization of human developmental, reproductive, immunological, and endocrinological hazard? What, if any, additional assumptions and uncertainties should EPA embody in these characterizations to make them more explicit?
Cancer effects	10. Do you agree with the characterization in this document that dioxins and related compounds are carcinogenic hazards for humans? Does the weight of the evidence support EPA's judgment concerning the listing of environmental dioxins as a likely human carcinogen?
	11. Does the document clearly present the evolving approaches to estimating cancer risk (e.g., margin of exposure and the lower limit on ED^{01} as a point of departure) as described in EPA's 1996 "Proposed Guidelines for Carcinogenic Risk Assessment"? Is this approach equally as valid for dioxin-like compounds? Has EPA appropriately reviewed, characterized, and incorporated the recent epidemiological evidence for cancer risk assessment for human populations?
	12. Please comment on the presentation of the range of upper bound risks for the general population based on this reassessment. What alternative approaches should be explored to better characterize quantitative aspects of potential cancer risk? Is the range that is given sufficient or should more weight be given to specific data sources?
Background and population exposures	13. Have the estimates of background exposures been clearly and reasonably characterized?
	14. Has the relationship between estimating exposure from dietary intake and estimating exposure from body burden been clearly explained and adequately supported? Has EPA adequately considered available models for the low-dose exposure-response relationships (liner, threshold, "J" shaped)?
	15. Have important "special populations" and age-specific exposures been identified and appropriately characterized?
Children's risk	16. Is the characterization of increased or decreased childhood sensitivity to possible cancer and noncancer outcomes scientifically supported and reasonable? Is the weight-of-evidence approach appropriate?
Relative risks of breast feeding	17. Has EPA adequately characterized how nursing affects short-term and long-term body burdens of dioxins and related compounds?

Topic	Question
Risk characterization summary statement	18. Does the summary and analysis support the conclusion that enzyme induction, changes in hormone levels, and indicators of altered cellular function seen in humans and laboratory animals represent effects of unknown clinical significance, but they may be early indicators of toxic response?
	19. Has the short summary statement in the risk and hazard characterization on page 107 adequately captured the important conclusions and the areas where further evaluation is needed? What additional points should be made in this short statement?
Sources	20. Are these sources adequately described and are the relationships to exposure adequately explained?

Source: EPA.

Appendix IV: EPA's Responses to Peer Review Panels

EPA generally addressed the peer review panels' comments by performing additional analyses, adding or revising text, or identifying comments as related to EPA's long-term research goals. In some instances, EPA thought that the reassessment already addressed the panel's comment. The panels classified their recommendations, suggestions, and concerns, and EPA responded to each. Tables 8 and 9 show the comments made by the panels and EPA's response or action taken.

Table 8: EPA's Responses to July 2000 Panel's Report

Recommendation	EPA response or action
1. Use terminology such as "ambient exposures" or "general population exposures," rather than the term "background exposure," which implies normal and acceptable.	EPA prefers to use "background exposure" as it appropriately recognizes the ubiquitous nature of trace amounts of dioxins in the environment and food supply even when no sources are identified nearby. EPA added a definition to its glossary.
2. Present more detail (e.g., sample calculations) in the *Integrated Summary* on exactly how the cancer slope factor was derived.	Additional information has been added to Section 5 of the *Integrated Summary* to clearly illustrate how the cancer slope factors were derived.
3. The panel thought that the upper bound cancer risk of 10^{-3} to 10^{-2} in the general population, implying an additional 3,000 to 30,000 deaths per year, was alarmist, not warranted and not realistic. Recommended that EPA should present "reality check" on the risk estimates relative to highly exposed past cohorts.	EPA states its estimates were derived from the best data sets available.
4. Include a table to summarize the various noncancer effects observed in animals and humans at low-level exposures.	EPA has added a table (table 2-2) to the *Integrated Summary* of the September 2000 draft. While not extensive, it illustrates the low range of margins of exposure that is calculated for a variety of effects in several species, including humans.
5.The panel thought body burden was an appropriate dose metric. However, the panel recommended that EPA explicitly explain the relationship among daily intake, serum levels, tissue dose, and body burden.	Additional discussion of alternative dose metrics has been included in the *Health Assessment of TCDD and Related Compounds* (Part II), Chapter 1: Disposition and Pharmocokinetics. This discussion has also been carried over to Section 1.3 of the *Integrated Summary*. The utility, strengths, and weaknesses of each are presented, and in a number of cases the relationships of one to another are discussed.
Suggestion	**EPA response or action**
1. Data presented on dioxin levels in food are an improvement over earlier drafts, but need more specific information on the number of samples collected, sampling locations, and standard deviations of observed levels presented in tables 4-6 and 4-8.	This additional information was included in *Estimating Exposure to Dioxin-Like Compounds* (Part I), Vol. 3, Chapter 4, and has been now added to the *Integrated Summary* (see table 4-5). This table presents dioxin levels in environmental media and food, along with number of samples, mean, range, and standard deviation.
2. Revise and expand discussion of dioxin levels in food, identifying levels of dioxins in other food sources for which data are available; listing food sources that have not been extensively characterized (i.e., fish); commenting on changing rate of dioxins in food sources over the years; and addressing the effects of cooking practices.	Several new paragraphs have been added/edited in the *Integrated Summary*, Section 4, to address these comments.

3. Reviewers thought EPA adequately derived approaches to estimate average daily dose from both dietary intake and body burden. Suggested revisions included (a) providing a clear definition of body burden and explaining how body burden relates to tissue levels; (b) presenting equations and sample calculations in the *Integrated Summary* to illustrate how average daily dose can be estimated from dietary intake or from body burden; (c) considering other sources of data for characterizing trends in body burden levels; and (d) providing additional detail on the variability in the distribution of estimated average daily intakes.	(a) EPA added a definition of body burden, and an explanation of how body burden relates to tissue levels, to the glossary in the *Integrated Summary*; (b) equations illustrating how average daily dose can be estimated from dietary intake or from body burden were in Part I, Vol. III, Chapter 4, but were not included in the *Integrated Summary* in the interest of brevity; (c) although body burden trends (e.g., differences in age) in the reassessment document are not statistically based, a current modeling study is underway to more fully understand body burden trends; (d) section 4.4.3 in the *Integrated Summary* on variability in intake levels has been expanded to include key references and a new discussion on the Center to Disease Control and Prevention blood study to further support the findings on variability. EPA is also currently investigating the possibility of using probability methods to further study variability of dioxin exposure.
4. Reviewers thought EPA identified important "special populations" of highly exposed individuals and suggested that the agency consider including others, such as people who lose weight rapidly, fetuses, and people who eat large amounts of potentially contaminated food sources not explicitly considered in the reassessment (e.g., lamb).	In Part I, Vol. III, Chapter 5, EPA analyzed a large amount of available data on these special populations: nursing infants (Section 5.2), people who fish (Section 5.3), people living near sources of dioxin release (Section 5.4), and cigarette smokers (Section 5.5). Other populations (such as exposed workers or those living in Seveso) were discussed in detail in Part II.
5. Reviewers thought EPA may have overstated upper bound risks and suggested EPA more clearly describe the basis of the current cancer slope factor and significance of upper bound cancer risks to public.	The text has been revised to put the upper bound estimate of risk in better perspective. The previous range of upper bound risks was apparently confusing and has been removed.
6. Most reviewers agreed that developmental, reproductive, immunological, and endocrinological noncancer effects could be seen in humans, given sufficient dose. Reviewers suggested EPA improve the justification for the conclusion that human epidemiological data suggest that noncancer effects occur at ambient exposures.	Additional discussion has been added to Sections 2,5, and 6 of the *Integrated Summary* to address this issue.
7. The panel thought the *Integrated Summary* presented a reasonable argument that cancer risk associated with breastfeeding is likely low and suggested EPA provide similar argument for noncancer effects.	EPA asserts that the argument that noncancer risk associated with breastfeeding is also low is already in the report, although it is not broken out into a separate section. EPA agrees with WHO that on balance, the benefits of breastfeeding outweighed risks of dioxin exposures.
8. The panel agreed that the *Integrated Summary* needs additional discussion on the uncertainties associated with using various dose metrics specifically for evaluating childhood risks. Some reviewers continued to have reservations about EPA's selection of the body burden dose metric for children, especially considering that children's (especially nursing infants') doses can be much higher than those of adults, even though their body burdens often are not.	See recommendation above relating to selection of a dose metric. Figures 4-4 and 5-2 were added to the *Integrated Summary* to help illustrate the rationale for selecting body burden as the dose metric using a nursing scenario, and expanded discussion can be found in Section 4. Nonetheless, uncertainty remains regarding the most appropriate dose metric for any given effect.
9. Most of the reviewers agreed with the use of margin of exposure to express exposures rather than comparing exposures with reference dose given the assumptions made in the assessment, but they suggested the implication of these assumptions be more clearly defined.	Additional discussion regarding the concept of margin of exposure has been included in Sections 5 and 6 of the *Integrated Summary*. A table has been added to illustrate the concept for several cancer and noncancer endpoints. Additional details have been added to the discussion regarding the decision to use a margin of exposure rather than calculate a reference dose.

10. The reviewers thought the *Integrated Summary* clearly presented the entire data set of dose response data that met EPA's selection criteria, but that presentation should be improved. Many thought that EPA should attempt to differentiate effects that are "frank manifestations of toxicity" from effects with unknown clinical significance.	Additional discussion has been added to the text to provide this differentiation, as suggested by the peer reviewers. EPA believes differentiating effects is inherently difficult since the manifestations of toxicological response lie along a continuum and biochemical changes may serve as a biomarker of the potential for frank response.
11. The reviewers generally agreed that Chapter 9 on TEQs in Part II, presented the history, rationale and support for the TEQ approach for evaluating dioxin toxicity, but they were concerned that this approach attributes dioxin toxicity to compounds for which few toxicologic data are available. Though the reviewers felt that Chapter 9 establishes clear procedures for using, calculating, and interpreting TEQs, they stated certain topics needed to be described more clearly and suggested EPA concisely state why it selected WHO's 1998 TEFs over previously used TEFs, present example TEQ calculations as an appendix, and should stress that risk assessors should characterize fate and transport of individual dioxins separately.	Chapter 9 on TEQs has been revised in response to peer reviewers' comments. Additional discussion has been added to the Chapter to focus on 5 compounds that make up greater than 70 percent of human exposure and body burden on a TEQ basis. While several of the minor compounds have limited toxicologic data supporting their TEF values, the major compounds have robust data sets. This discussion has been carried over to the *Integrated Summary* in Section 1.2.

Source: EPA.

Table 9: EPA's Responses to Science Advisory Board Panel's Comments

Recommendation	EPA action or response
1.Carry out additional work on the exposure assessment section to evaluate sources that make the greatest contribution to dioxins in the food chain, and make the text consistent with the tables.	This is a long-term research goal of EPA. EPA officials stated that they interpret the Science Advisory Board recommendation as basically endorsing what EPA plans to do in the future—linking sources of dioxins with exposures. The minor issue regarding making the table and text consistent was resolved by EPA.
2. Include discussion of all "special population" exposures in the summary document.	EPA added additional information regarding "special population" exposures (i.e., some Native American subsistence fishers could be highly exposed to dioxins depending on the amount of fish they catch and where). According to EPA officials, the agency now addresses this issue in the *Integrated Summary* —Sections 4 (exposure) and Section 6 (risk characterization) and specifically mentions Native Americans in the text.
3. Extend breastfeeding exposure scenarios beyond 1-year.	According to EPA officials, they performed additional analysis and revised the related text. See *Integrated Summary*, Section 6.
4. For human carcinogen designation, better understanding and interpretation of epidemiological data are needed. Add expected differences in results between epidemiological studies of genotoxic agents and cancer promoters.	EPA added text in Part II and the *Integrated Summary* regarding the expectations for epidemiological studies for strong cancer promoters and will be including a discussion of new cancer studies in the reassessment to provide the latest on this issue.
5. Methodology: Agree with use of margin-of-exposure approach, but in addition calculate a reference dose.	EPA disagreed and chose not to calculate a reference dose, but explanation of why it did not explained in more detail. See pp. 118-122 in the *Integrated Summary*.
6. Methodology: In future reevaluations develop quantitative estimates of noncancer risk—similar to those developed for cancer— to the extent methods become feasible.	EPA's opinion is that to some extent it is already merging cancer and noncancer methods using margin-of-exposure analysis for both cancer and noncancer effects. The text tries to balance the discussion of cancer and noncancer risks, but noncancer risks cannot be done quantitatively.

7. Further investigation of noncancer hazards is needed. They receive insufficient attention on pp. 7 and 11. About half of the panel believes that the current draft assessment may overestimate the likely cancer hazard.	EPA revised the text to put noncancer effects into better perspective, but officials acknowledged that the tools used to describe cancer risks are easier for people to understand. In the text of the report, EPA is providing more discussion on noncancer effects by providing examples where possible.
8. The panel agreed with using body burden as the dose metric; however, better justification for using a specific dose metric such as body burden is needed. Provide more explicit examples of how different dose metrics might apply to specific toxic endpoints.	EPA officials said that the agency has revised and added text in several places to better explain the variety of dose metrics available and why body burden is the best choice for assessing dioxin. EPA revised Part II, Chapter 1 on dose metrics and it also made changes to Chapter 8 and added text in the *Integrated Summary*, Sections 1,5, and 6. EPA recognized the need to better explain that using other dose metrics rather than body burden in certain situations is also acceptable.
9. EPA should identify important data gaps on body burden (i.e., how it varies with age and in females depending on number of offspring) to highlight research opportunities.	EPA officials stated that research opportunities in the future will address this issue. EPA will be incorporating new studies in future dioxin assessments, particularly those that look at population dynamics (i.e., younger people starting now with lower intake levels /body burdens than in past) as they become available. Currently, there is major work under way at the Center for Disease Control and Prevention looking at serum levels regarding dioxins and other health issues that will give insight /data on body burdens. First-year data of 3-year study have been collected.
10. There is some evidence that very low doses of dioxins may result in some decreases in adverse responses but can produce other adverse effects at the same or similar doses. Evaluate the totality of the evidence for non-monotonic dose response as studies become available, particularly evidence for any "U-shaped" dose response curve.	EPA officials stated that the agency will continue to work on the dose response chapter. The possibility that dioxins are anti-carcinogen is reflected in the *Integrated Summary*, Section 2 with three Kayajanian references. However, EPA does not have data on where or if it occurs on the dose response curve—above or below body burdens.
11. Calculate ED using definitions other than that used for ED^{01} and for comparison purposes present values of ED^{10} (since its been applied to other chemicals by the agency).	EPA has done additional analysis using other effective dose values (e.g., ED^{10}). EPA officials stated that it differed from the original calculation using ED^{01} in only a few instances. See pp. 118-122, in *Integrated Summary* and Part II, Chapter 8.
12. Give additional consideration to its justification of method selection for condensing these effective doses into a recommended range.	See #11 above.
13. The agency's description of its calculation of ED^{01} was not sufficiently detailed to permit the calculations to be repeated. Describe calculation of ED^{01}more clearly and completely.	More explanation provided for use of ED^{01}. See #11 above.
Suggestion	
1. The agency's calculation of the cancer potency factor is not prominently featured in the reassessment. Highlighting this calculation would significantly improve the transparency and accessibility of the reassessment.	EPA officials disagreed with the comment that cancer potency factor not prominently featured. EPA officials stated that figure (5-2) on cancer potency estimates for animal studies with full page footnote provided in version reviewed by the Science Advisory Board. Text has been added in Part II, Section 5 discussing sensitivity of calculations.

2. The panel suggested that the agency consider making greater and more systematic use of parametric methods in calculations. This approach would help readers to develop a better sense of how the results presented depend upon specific analytical assumptions.	EPA does not plan to perform additional analysis. This is mostly intended as a recommendation to do further research.
Concern	
1. The majority of panel members have concerns about Agency cancer risk estimates associated with current population exposures and feel that it was not appropriate for the agency to characterize the risks in such a quantitative manner without providing a similar quantitative estimate of uncertainty.	EPA has added text on what EPA can say about quantifying uncertainty. EPA officials agree with the Science Advisory Board that there needs to be improvements in methodology (i.e., it will require more/better data sets). However, this will require further research in the future. It is a generic concern, not just regarding dioxins.

Source: EPA.

Appendix V: Comments from the Environmental Protection Agency

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 17 2002

OFFICE OF
RESEARCH AND DEVELOPMENT

Ms. Christine Fishkin
Assistant Director
Natural Resources and Environment
United States General Accounting Office
Washington, DC 20548

Dear Ms. Fishkin:

I am writing in response to an April 5, 2002 letter from David G. Woods to EPA Administrator Christine Todd Whitman transmitting the draft General Accounting Office (GAO) report entitled, Environmental Health Risks: Information on EPA's Draft Reassessment of Dioxins (GAO-02-515) for Agency review. Thank you for the opportunity to provide our comments on this report before it is issued in final form. I realize that this report is the culmination of a significant effort by you and your colleagues. You should be commended for your thorough researching of the questions posed to you and your balanced treatment of the information at your disposal. This 67 page report deals with technically complex issues which you have succeeded in presenting in a concise and logical document. Your involvement of Agency experts in the information gathering and drafting phases of this report has no doubt added to its success and I compliment their efforts as well.

While the Agency is very pleased with this draft report. Some of the points made by the Agency have not found their way into this review draft. The Comments provided below represent a series of issues where additional Agency comment is considered necessary. We have also provided a mark-up noting minor or editorial corrections for your consideration. These comments are not meant to detract from the overall quality of the report but are presented for clarification and completeness.

See comment 1.

1) Apparent inconsistencies among different components of the Draft Reassessment Documents: The GAO was supplied with internal working copies of all components of the draft EPA dioxin reassessment. Each of these components was undergoing revision in response to comments from an independent peer review panel and the EPA Science advisory Board (SAB). At the time of the GAO review, different components were at different stages of revision. The exposure information contained in the Risk Characterization is a summary of information and analysis presented in the Exposure and Health Volumes. Since the development of the working draft of Characterization follows development of the working draft of the Exposure and Health Volumes, some inconsistences are inevitable. Among the changes made in the Exposure Volume that were identified as inconsistences by the GAO are the refinement of the fat content of

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ingested products, and the introduction of an additional category of consumption called "other meats". Clearly, it is EPA's intent to make the documents fully consistent at publication. In identifying these inconsistencies without clearly explaining the sequential nature of the revision process, the GAO report could lead some readers to interpret these as significant flaws rather than simply an issue of the draft Characterization not yet reflecting the updated Exposure Volume. The locations and text in question follows:

a. Footnote on p. 8: "EPA's *Integrated Summary* (Table 4-7) presents information on exposure to 9 foods...." Table 4-7 in the draft Integrated Summary had not been updated yet.
b. p. 19: The Integrated Summary does not reflect the newer and more valid percentages of fat in the food products found in the Exposure Volume.
c. p. 22: The Integrated Summary does not include corrected average percent fat in milk found in the Exposure Volume.

See comment 2.

2) Characterizing potential sources of uncertainty in the draft Reassessment's dietary exposure estimate: The GAO draft correctly identifies several sources of potential uncertainty in the reassessment's estimate of dietary exposure. Each of these uncertainties is also identified in the draft reassessment. In our view, this point is not emphasized sufficiently in the GAO draft report. More importantly, the GAO report does not provide the reader with enough perspective to judge the relative significance of these uncertainties to the overall calculation of dietary exposure. Without such a discussion, many readers would reasonably conclude that the uncertainties are of significance; otherwise, GAO would not have emphasized them. This is not the case. Three issues are of particular importance are: a. The strength of the food concentration data for deriving national mean levels of exposure; b. The sampling of adipose tissue rather than muscle tissue in the meat surveys; and, c. The likelihood that current dioxin levels in food have significantly declined since the mid-nineties. EPA does not believe that these three issues raised are major weakness in the dietary exposure calculation. EPA has discussed in detail each of these issues with the GAO review team. However, the current draft of the GAO report does not adequately capture the depth of those discussions. A more detailed discussion of these issues follows.

See comment 3.

Now on p. 10.
See comment 4.

a. The draft GAO report states on p. 11, 1st sentence in second paragraph: "... dioxins vary and acknowledged that the available studies generally were not designed to estimate national exposures." This is incorrect. The reassessment's dietary estimate for beef, pork, and poultry are all based on joint EPA/USDA studies which incorporated a rigorous statistical design specifically intended to derive a representative national mean concentration. Estimates for milk and dairy were based on an EPA milk survey that had broad national coverage. Although not a statistically based sampling, the study was specifically intended to gather milk samples that were representative of typical milk consumed in the US. Fish and shellfish accounted for an additional 26 % of national exposure and this analysis relied on data from a wide variety of sources not intended to develop a national mean. Data on eggs, which the GAO study reviews in detail, account for only 4% of the total and were not part of a formal national survey. Together beef, pork, poultry, milk and dairy account for 66% of total estimated exposure; consequently, a majority of the dietary exposure estimated

by EPA was derived from studies specifically designed to estimate national exposures. Fish is the one major food category, not based on sampling, designed to generate a national exposure mean.

b. p 12, 2nd bullet and p. 17, 1st bullet: Concern is expressed about the comparability of grocery store samples and the fat reservoir samples taken for beef/pork/poultry in the national surveys: "Some of the samples are of edible food products sold in grocery stores, while others are of inedible cuts of fat, such as back fat on cattle...." The three national surveys obtained back fat from cattle, leaf fat from poultry, and belly fat from pork for the reasons this report cites on p.17. "EPA used this approach because USDA federal inspectors could obtain the samples with little disruption to the slaughtering establishments and because the samples' high fat content would enable more accurate measurement of dioxins, since the analysis would be of highly concentrated fat samples....EPA concluded that the fat samples for all three foods were comparable ."

Now on p. 14.
See comment 5.

The use of the term 'inedible fat' may be misleading to some readers. The term, as used in the reassessment, refers more to the marketability of the fat rather than its physiological or nutritional status. For example, the back fat taken from beef carcasses is the same fat reservoir that extended to the ribs, which is considered edible fat. The critical issue is whether the lipid-adjusted concentrations of dioxin-like compounds of the sampled adipose tissues are good indicators of the lipid adjusted concentrations found in muscle tissues regularly consumed in the US diet. EPA has concluded the answer to this question is an unequivocal yes. There is a well developed understanding of distributional behavior of dioxin-like compounds in vertebrate tissues. In general, dioxin-like compounds distribute readily across the fat reservoirs of an organism, based on tissue lipid concentration. This understanding served as an essential component of support to the reassessment's broader conclusion that body burden is the best dose metric for estimating risk. This position was endorsed by the EPA, SAB and is also the position adopted by the WHO.

Now on p. 15.
See comment 6.

EPA chose to further support this understanding by specifically examining dioxin distribution in beef cattle. The GAO draft report discuses this study on p. 17, stating that "For the five samples, the ratios of CDDs and CDFs in muscle fat to CDDs and CDFs in back fat varied by up to 300 percent, ranging from 0.58 to 1.7; and the ratios for PCBs varied by up to 50 percent, from 1.0 to 1.5. This variability indicates that using fat samples may overstate or understate dioxin levels in beef, pork, and poultry to some extent." This GAO interpretation fails to adequately take into consideration the inherent variability that comes from trying to measure 0.000000000001 grams of dioxin in a gram of fat. Given the complexities of dioxin laboratory analysis, back fat concentrations ranging from ½ to 2 times the concentration in edible fat is best characterized as indistinguishable from each other. The full weight of evidence provides strong support for the use of back fat data to calculate dietary intakes for beef.

c. The Draft GAO review correctly reports that most of the food concentration data used in the reassessment were collected between 5 and 8 years ago and that since that time emissions from regulated sources are anticipated to have declined (P11 first bullet and

Now on p. 37.
See comment 7.

footnote 10 , p 44 observations). On page 45, the draft report concludes that "the extent to which estimates accurately reflect current average daily exposure is not known". EPA believes that sufficient information is available to support a conclusion that, in spite of the emission reduction of the late 1990's, the exposure estimates of the draft reassessment are a reasonable characterization of contemporary exposure. The dioxin reassessment emissions inventory estimates that, from 1987 to 1995, overall quantifiable releases to the environment decreased by 75%. Most of this reduction was from municipal and medical waste incinerators and from pulp and paper facilities use of chlorine bleach. These reductions were, in large part, in anticipation of EPA's promulgation of regulations scheduled for the last half of the 1990's. EPA has projected that full implementation of these rules would result in an overall decrease in quantifiable emission from the 1987 baseline of 90% or an additional 15% increment over the 1995 decline level. Most of the food samples were taken after the initial 75% decrease had occurred and therefore much of the decrease should already be reflected in the food concentration numbers. Additionally, most of the municipal and medical waste incinerators are located far from, and down-wind from, concentrated meat and dairy production areas; consequently, the impact of these emissions reduction on the commercial food supply should be less than directly proportional to their reduction in overall environmental release. Finally, reservoir sources of dioxin-like compounds (old releases that have been stored in soil and sediment and then reintroduced to the environment) are estimated to account for half or more of current exposure. This, combined with the unquantified sources of dioxin that cannot be accounted for in the inventory estimate, tend to reduce the likelihood of emission reduction in the late 90's significantly affecting the current estimate of general population exposure via the commercial food supply. EPA has concluded that, looking at the full weight of the evidence, exposure estimates based on food concentrations for the mid-1990's should be representative of current dietary exposure.

See comment 8.

3) Variability in dairy concentration data: On p. 22 GAO, correctly describes the variability in dairy products reported in the Oct. draft. EPA has reviewed this number and concluded that since dairy lipid-adjusted concentration is derived directly from the milk data it should not have a separately derived standard deviation. The milk values are as reported in the GAO review (0.18 plus or minus 0.0012). This change was verbally reported to the GAO review team.

Now on p. 15.
See comment 9.

4) Exclusion of elevated poultry samples form mean concentration calculation:
Page 18 of the draft GAO report reads: "EPA considered the two poultry fat samples inappropriate for the dioxins study, which was aimed at identifying typical exposures to dioxins. However, it is not clear that the poultry samples with high concentrations of dioxins were anomalies because the incidence of dioxin contamination in animals feeds is not known." EPA has reported to the GAO review team that the cause of the high poultry samples was specifically determined to be because of localized use of ball clay as an anti-caking agent in soybean meal. That ball clay is no longer being used (voluntarily removed after a FDA request to feed manufacturers). EPA concluded it was inappropriate to extrapolate the ball clay samples nationally to describe current background exposures via consumption of poultry. EPA is currently drafting a new section on animal feed contamination episodes, to include more details of this episode.

See comment 10.

5). **Percentage of fat in consumed product:** On p. 15, 2nd bullet, GAO states that, "...specific information on the assumptions and analyses EPA used in estimating these average fat percentages is not provided in the draft reassessment report." On p. 19, this same point is made, but in more critical detail. This is not correct. On p. 3-73 of the draft Exposure Volume, EPA provides the following explanation for their procedure for estimating percentage fat in consumed beef:

> The percentage of fat in beef was estimated using food consumption data and fat content data for various beef products provided by David Haytowitz, USDA, to Linda Phillips, Versar, Inc., by personal communication, January 2001. USDA obtained food consumption data from the 1994-96 Continuing Survey of Food Intake Among Individuals (CSFII). The total quantity (in grams) of each food item eaten by the survey population in one survey day was tabulated and weighted to represent the quantity eaten by the entire U.S. population in one day. The fat content of each of these food items was also reported. To estimate the weighted mean percent of fat in beef products that are typically consumed by the U.S. population, the total amount of each beef item was first multiplied by the fraction of fat reported for that item to calculate the amount of beef fat consumed from each beef item. Next, the total amount of beef fat consumed (in grams) was calculated by summing the beef fat intakes for the individual beef items. The total amount of beef consumed was also estimated by summing the beef intake for the individual beef items. Finally, the weighted fraction of beef was estimated by dividing the total beef fat intake by the total beef intake. An abbreviated (i.e., the total number of beef items included in the analysis was 146; only a few beef items were included in the example to demonstrate the methodology) example of this calculation is provided in Table 3-39.

It was also stated that the same source of data and procedure was followed for poultry and pork, though without this much detail. EPA is considering adding this information as an appendix to the Exposure Volume.

6) **Comparison of dietary intakes with body burden:** The GAO report focuses on the reasonableness of the dietary intake estimates by examining the uncertainties in national food level data and dietary intake assumptions. There is, however, an additional analytic approach provided in the reassessment to assess the reasonableness of dietary estimates that is not acknowledged by the GAO. This is the comparison of projected intake levels to body burden measurements. For persistent bioaccumulating compounds, scientists can use human tissue measurements (blood serum) and pharmacokinetic modeling to estimate cumulative exposure. Using this approach, the reassessment concludes that when past elevated environmental levels are taken into consideration there is strong agreement between current measured serum levels and current estimated dietary exposure.

7) Instances of data not supplied in the draft report:

a. Other meats: On p. 13 and the footnote on p. 15, it is stated that EPA did not provide data on the concentration and composition for "other meats". The footnote on Table 4-30 from the October 2001 draft states that the concentration of 0.18 ppt assigned to "other meats" was, "estimated as the average of beef, pork, and poultry." The justification and exact procedure for doing this will be included in the final draft of the Exposure Volume.

b. Number of samples in composite for PCB analysis: On p. 14, it is noted that, "The draft reassessment report does not specify the number of individual samples in the composite samples" for egg, fish, freshwater fish and shellfish, and vegetable. All these data was from two publications from Mes, and Mes and Weber. These individuals did not specify in their publication how many samples were in the composites. A sentence will be added to the description of the data stating that they did not identify how many samples were in the composite.

See comment 11.

8) Peer Review Process: Page 4, para 2, line 4 of the draft GAO report reads "12 reviewers assembled by EPA" . The reviewers are not chosen by EPA, but by an independent contractor (as noted by GAO later). It is important to be clear that in all instances, peer reviewers were chosen by an outside party, not EPA, in keeping with EPA's Peer Review Guidance.

Now on p. 6.
See comment 12.

9) TEF Values: The TEF for 2,3,4,7,8-PeCDF is 0.5. Therefore, the statement in the 4th line from the end of the middle paragraph on page 6 of the draft GAO report needs correction to note that PeCDD has a TEF of 1.0, PeCDF has a TEF of 0.5; all the others have TEFs of 0.1 or lower.

Now on pp. 20-21.
See comment 13.

On p.25, last line of 1st paragraph, the GAO Report suggests that TEFs for cancer rely on non-cancer endpoints. TEFs are relative potency factors which are independent of endpoint. This is a basic underpinning of the entire TEF approach. All data are considered, according to a weighting scheme derived by international consensus and based on scientific judgment, in setting TEFs. While EPA recognizes that there are few long term carcinogenesis studies for other dioxins, there are many studies of tumor promotion data demonstrating that the TEFs work for that endpoint. GAO, EPA and peer reviewers of the EPA reassessment have recognized that further research on TEFs for dioxin and related compounds is needed. Some of this work is ongoing and will provide input into future TEF updates.

In conclusion, I want to reiterate that the above mentioned discussion is meant to provide clarification and completeness to a well researched and written report. Thank you for the opportunity for the Agency to provide these comments as the GAO moves toward finalizing its Report.

Sincerely yours,

Paul Gilman
Assistant Administrator

Attachment

The following are GAO's comments on EPA's letter dated April 17, 2002.

GAO Comments

1. The discrepancies we identify between the *Integrated Summary* and supporting chapters appear in the October 2001 reassessment documents that EPA distributed for internal agency review. We identified them primarily to inform readers of our report of the source of the information we cite. For example, a reader of the *Integrated Summary* would find (outdated) information on 9 food types, whereas we are citing information on 10 food types that is provided in the supporting chapters of EPA's reassessment documents and that EPA officials told us is correct.

2. Throughout the section of our report on EPA's estimate of dietary exposure to dioxins, we attribute the identification of the limitations to EPA's draft reassessment report.

3. Our report did not characterize the significance of the limitations EPA identified in its reassessment documents. We have added to the report EPA's opinion that these limitations do not represent major weaknesses in its estimates of dietary exposure to dioxins.

4. The statement in our report that that the available studies generally were not designed to estimate national exposures is derived from page 76 of EPA's October 2001 *Integrated Summary* draft. In this document EPA says: "The amount and representativeness of the data vary, but in general these data were derived from studies that were not designed to estimate national background means." In its written comments, EPA says that most of the dietary exposure it estimated was derived from studies specifically designed to estimate national exposures. In support of this point, EPA says that 66 percent of the estimated exposure to dioxins is from eating beef, pork, poultry, milk, and dairy products, and that these studies were designed to estimate national exposures. (We note that these studies cover 5 of the 10 food types on which EPA based its exposure estimates.) Importantly, our draft report stated that the studies on beef, pork, and poultry were based on the first statistically designed national surveys of dioxin levels in these foods and that the milk samples upon which both the milk and dairy estimates were based came from a national survey with samples collected from sampling stations in a majority of the states. However, while our review of EPA's milk survey design plan indicated the milk samples were intended to assess the levels of dioxins in the general milk supply of the United States, the survey design document also stated that (1) the milk would be collected from dairy plants around the United States that represent approximately 20 percent of the nation's milk supply

and (2) the survey was not designed to be statistically rigorous—that is, it was not intended to randomly sample milk in such a way that the results could be generalized to the full milk supply with a known degree of precision. Thus, we concluded that EPA's statement in the *Integrated Summary*—that the studies covering the 10 food types generally were not designed to estimate national exposures—was accurate. In light of EPA's comments and the fact that the milk samples used to estimate milk and dairy exposures did have national coverage, we have revised the report to indicate that EPA acknowledges that some of the available studies were not designed to estimate national average exposures.

5. We revised the description of the fat samples from "inedible fat samples" to cuts of fat, such as back fat on cattle, that generally are not consumed by the U.S. public.

6. We understand that there is variability associated with measurements at the picogram level. Nonetheless, we continue to believe that the variability identified among the five samples studied indicates that using fat samples not consumed by the public may overstate or understate to some extent dioxin levels in beef, pork, and poultry products sold to the public.

7. In its comments, EPA stated that it believes that sufficient information is available to support a conclusion that, in spite of the emission reduction of the late 1990s, the exposure estimates of the draft reassessment are a reasonable characterization of contemporary exposure. We have revised the report to include EPA's opinion and the reasons it cited in support of its view that the emission reduction in the late 1990s does not significantly affect the current estimate of general population exposure. However, because EPA does not have data on dioxin emissions after 1995, we cannot evaluate EPA's conclusion.

8. EPA stated that it plans to delete information on the variability in dairy concentration data from the reassessment report, and we have therefore deleted this point from our report.

9. We understand that the contamination of the two samples eliminated from EPA's estimate was found to stem from a localized ball clay contamination. However, we continue to believe that because of the lack of information on the incidence of dioxin contamination in animal feeds as well as on the potential sources of such contamination, it is not clear that the poultry samples with high concentrations of dioxins were anomalies. For example, this animal feed contamination problem was identified as a

result of the first national survey of only 80 poultry fat samples. We acknowledge that a decision to exclude apparently anomalous information entails professional judgment. However, because the incidence of contamination of animal feed is unknown, we believe that it is important for users of the dioxin reassessment to understand the judgments EPA made in estimating dietary exposure.

10. In the draft report, EPA does not provide information on the assumptions and analyses used to estimate the average fat percentages for pork and poultry. However, EPA does provide some information on how it estimated the fat percentage for beef. The fat percentage estimates affect the exposure estimates, and we believe this information should be included in the reassessment report. In its comments to us, EPA stated that the agency is considering adding information about the pork and poultry estimates to the report. We are therefore deleting references to this point in our report.

11. We deleted the phrase "assembled by EPA" to be consistent with information we provide in the body of the report that the peer review panelists were selected by an independent contractor.

12. We have revised this statement to reflect the fact that most (rather than all) of the other dioxins have TEFs of 0.1 or lower.

13. We clarified that TEFs apply to all effects, not just those for which relative potency data were available.

Appendix VI: GAO Contacts and Staff Acknowledgments

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Other key contributors to this report include Timothy Bober, Greg Carroll, Nancy Crothers, Greg Wilmoth, and Carrie Wheeler.

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