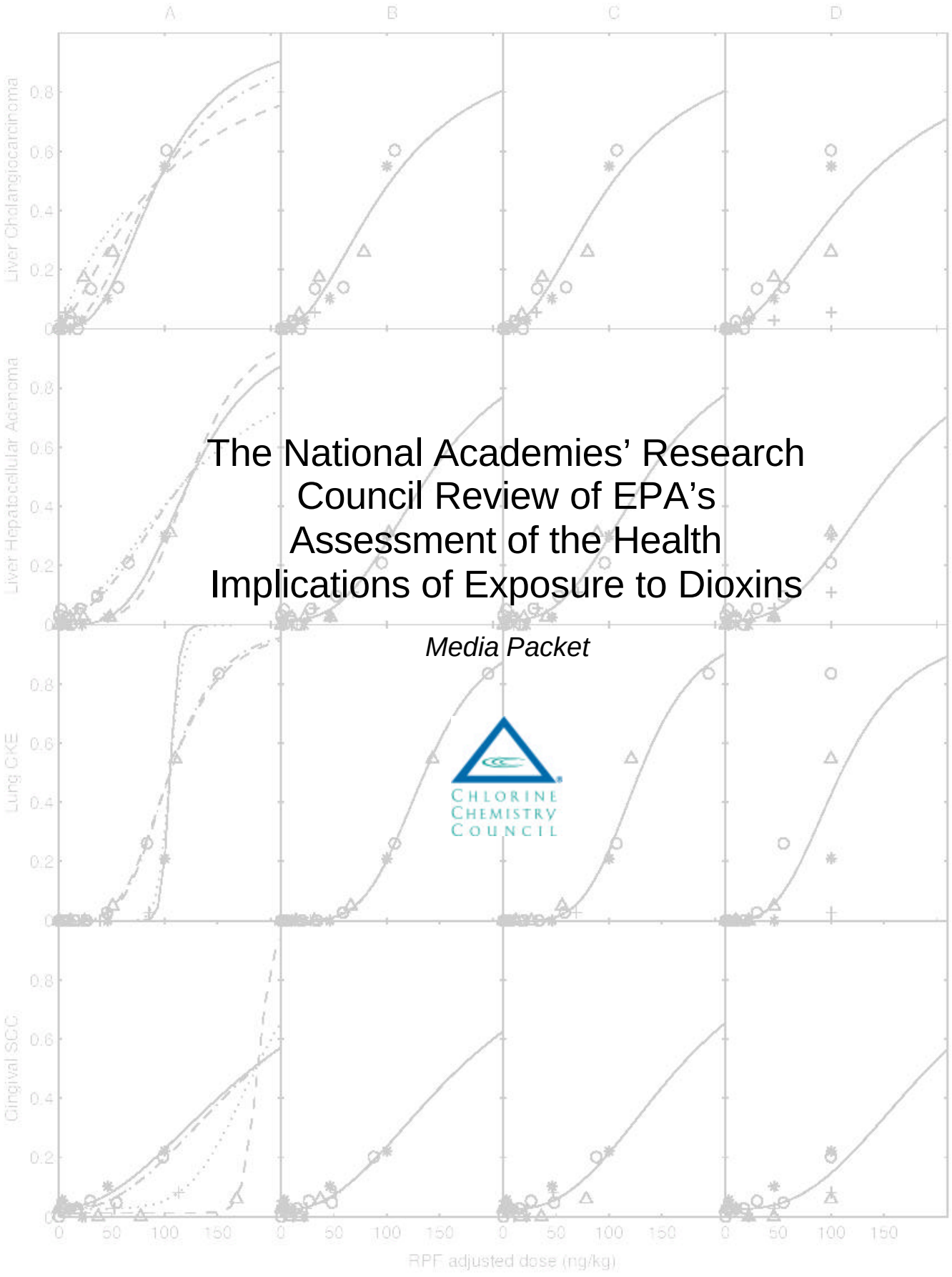
The National Academies' Research Council Review of EPA's Assessment of the Health Implications of Exposure to Dioxins

Media Packet

CHLORINE CHEMISTRY COUNCIL



Non-linear cancer dose-response curves from Walker *et al*., (2004)
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Why has The National Academies Research Council (NAS) been asked to review the EPA's Dioxin Reassessment?

There is a wide discrepancy between the draft dioxin risk characterizations of the U.S. Environmental Protection Agency (EPA) and those of respected public health agencies, such as the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), the Joint United Nations Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) and the European Commission Scientific Committee on Food (EC SCF). EPA uses very conservative assumptions and policy positions to arrive at a dioxin risk characterization that is 100 to 1,000 times more conservative than those of the other three agencies.

EPA consulted with the Interagency Working Group on Dioxin[1] (IWG) on its draft dioxin reassessment. Based on that consultation, the EPA, and other members of the IWG asked the NAS to provide an additional review to help ensure that the risk estimates contained in the draft are scientifically robust and that there is a clear delineation of all associated uncertainties. The EPA is to review the draft report in light of the NAS comments and will make appropriate revisions to the draft to address those comments. This review includes "charge" questions that go to the fundamental underpinnings of the science of the reassessment, such as: EPA's cancer risk estimates; whether human studies support EPA's risk conclusions; and the agency's method for comparing the toxicity of dioxin congeners through the use of toxic equivalency factors.

Aspects of The National Academies' Research Council Review of EPA's Assessment of the Health Implications of Exposure to Dioxins

The NAS committee is asked to focus primarily on Part III, the risk characterization section, of the reassessment. According to the specific **Charge Questions,** the committee will:

1. Examine the scientific evidence for classifying dioxin as a human carcinogen and the validity of the non-threshold linear dose-response model used by EPA;
2. Provide scientific judgment regarding TEFs and the uncertainties associated with them;
3. Review the uncertainty associated with EPA's approach to analysis of food sampling and human dietary intake data; i.e. human exposures;

Continued…

[1] Interagency deliberations include EPA science managers and representatives of the Departments of Health and Human Services, Agriculture, Veterans Affairs, Defense, State and the Executive Office of the President.

4. Review the uncertainty and variability associated with risk assessment decisions and numerical choices; e.g. modeling assumptions associated with the dose-response curve and points of departure;
5. Identify gaps in scientific knowledge critical to understanding dioxin reassessment.

##

Key Science Elements for the Committee's Consideration From the Chlorine Chemistry Council's Perspective:

1. A threshold approach is appropriate for addressing the potential carcinogenicity of dioxin.
2. Non-cancer endpoints should be accorded more weight.
3. The use of TEFs should be subjected to a more rigorous and current scientific review to assure the associated uncertainties are recognized and accounted for in their use in judging risk.
4. Dioxin emissions, and subsequently levels in the environment and food, continue to fall, therefore more recent exposure level determinations need to be taken into account in the reassessment.

Key Science Element #1: **A threshold approach is appropriate for addressing the potential carcinogenicity of dioxin.**

Although many laboratory animal studies support a threshold model for dioxin cancer effects [2], the U.S. Environmental Protection Agency (EPA) adheres to a linear, no-threshold model as a matter of policy. The Joint United Nations Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) and the European Commission Scientific Committee on Foods (EC SCF) have examined the weight of scientific evidence and endorsed a threshold model of dioxin cancer effects. In contrast, EPA assumes that any amount of dioxin, no matter how small, poses some degree of cancer risk.

That EPA continues to model dioxin cancer effects using no-threshold linearity is inconsistent with its recognition of dioxin as a cancer promoter, and not a cancer initiator. The Science Advisory Board was critical of EPA's modeling approach, citing the apparently non-linear nature of some of the carcinogenic data and the widely accepted biological argument that receptor-mediated carcinogens may feature non-linearities or even strict thresholds (EPA, 2001).

Agency for Toxic Substances and Disease Registry scientists also question EPA's assumption that dioxin's health effects are linear and without a threshold, stating, "…the primary basis for the threshold assumption is the premise that a physiological reserve exists within an organism and within organ systems that must first be depleted before the onset of toxicity or clinical disease. The implication that the threshold is simply a policy position is not consistent with this physiological principle" (Pohl et al., 2002).

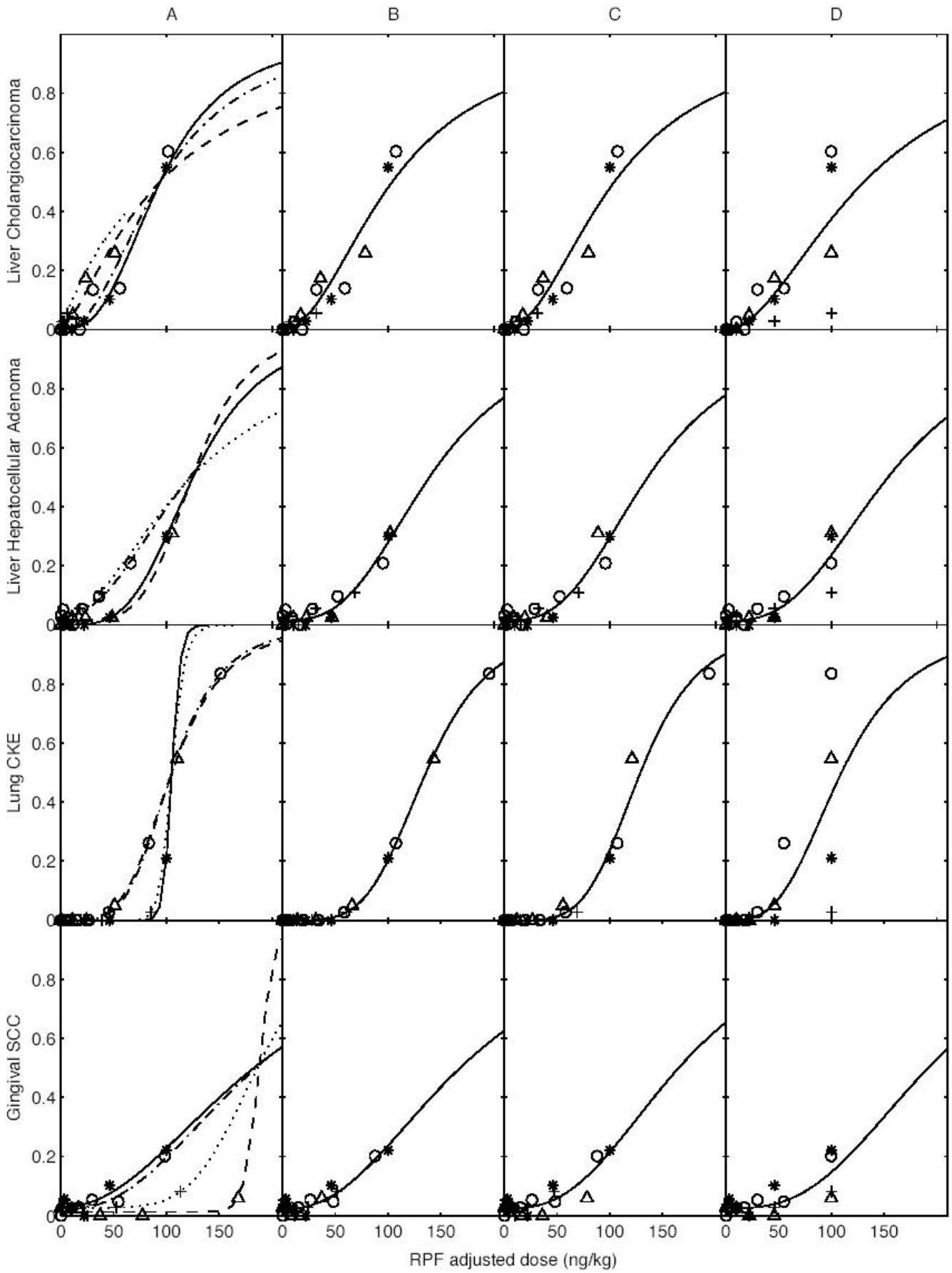
In a July 7, 2000, letter responding to the EPA's July, 2000, draft dioxin reassessment, two of the authors of the Dose-Response Modeling chapter, Drs. Rory Connolly and Melvin Anderson, expressed their concern that "…the data

[2] These studies include: Turtletaub et al. (1990), Randerath et al. (1988), Wassom et al. (1977), Kociba (1984), Giri (1987) and Shu et al. (1987).

available on liver tumor promotion [in animals] and regional enzyme induction strongly support non-linear relationships for enzyme induction and liver cancer. For us this is not just a plausible alternative, but also a preferred hypothesis with extensive experimental support."

Finally, in a recent experimental study, a team led by Dr. Nigel J. Walker examined dose additive cancer effects in rodents receiving TCDD, PCB 126 and PeCDF and mixtures of these dioxin-like compounds ("Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds," *Environmental Health Perspectives*; Oct. 19, 2004, available at http://dx.doi.org/). Dose-response curves for all cancers studied were characterized as "highly non linear" (p. 13). These curves are reproduced on the next page and in a watermark on the front cover of this packet.

In the face of significant scientific evidence to the contrary, EPA's policy decision to adhere to a linear, no-threshold model of cancer risk is unsupportable.



Non-linear cancer dose-response curves from Walker *et al*., (2004)
Reprinted with permission from *Environmental Health Perspectives*

References:

Giri, A.K. (1987). Mutagenic and genotoxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin: A review. Mutation Research 168, 241-8.

Kociba, R. (1984). Evaluation of the carcinogenic and mutagenic potential of 2,3,7,8-TCDD and other chlorinated dioxins. In Poland, A. and Kimbrough, R. (Eds.), Banbury Report 18: Biological mechanisms of dioxin action (pp.73-84). Cold Spring Harbor, New York: Cold Spring Harbor Laboratory.

Pohl, H.R., Hicks, H.E., Jones, D.E., Hansen, H., and De Rosa, C.T. (2002). Public Health Perspectives on Dioxin Risks: Two Decades of Evaluations. Human and Ecological Risk Assessment, 8, pp. 233-250.

Randerath, K., Putman, K.L., Randerath, E., et al. (1988). Organ-specific effects of long-term feeding of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 1,2,3,7,8-pentachlorodibenzo-p-dioxin on I-compounds in hepatic and renal DNA of female Sprague-Dawley rats. Carcinogenesis 9, p. 2285-89.

Shu, H.P., Paustenbach, D.J. and Murray, F.J. (1987). A critical evaluation of the use of mutagenesis, carcinogenesis and tumor promotion data in a cancer risk assessment of 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin. Regulatory Toxicology and Pharmacology 7, pp.57-8.

Turteltaub, K.W., Felton, J.S., Gledhill, B.L., et al. (1990). Accelerator mass spectrometry in biomedical dosimetry: Relationship between low-level exposure and covalent binding of heterocyclic amine carcinogens to DNA. Proceedings of the National Academy of Sciences of the USA, 87, 5288-92.

U.S. EPA Science Advisory Board (2001). Dioxin Reassessment: An SAB Review of the Office of Research and Development's Reassessment of Dioxin; Review of the Revised Sections.

Walker, N.J., Crockett, P., Nyska, A., Brix, A., Jokinen, M.P., Sells, D. M., Hailey, J.R., Easterling, M., Haseman, J.K, Yin, M., Wyde, M.E., Bucher, J.R. and Portier, C.J., (2004). Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds," *Environmental Health Perspectives*; Oct. 19, 2004, available at http://dx.doi.org/

Wassom, J.S., Huff, J.E. and Loprieno, N. (1977). A review of the genetic toxicology of chlorinated dibenzo-*p*-dioxins. Mutation Research 47, 141-60.

Key Science Element #2: **Non-cancer endpoints should be accorded more weight.**

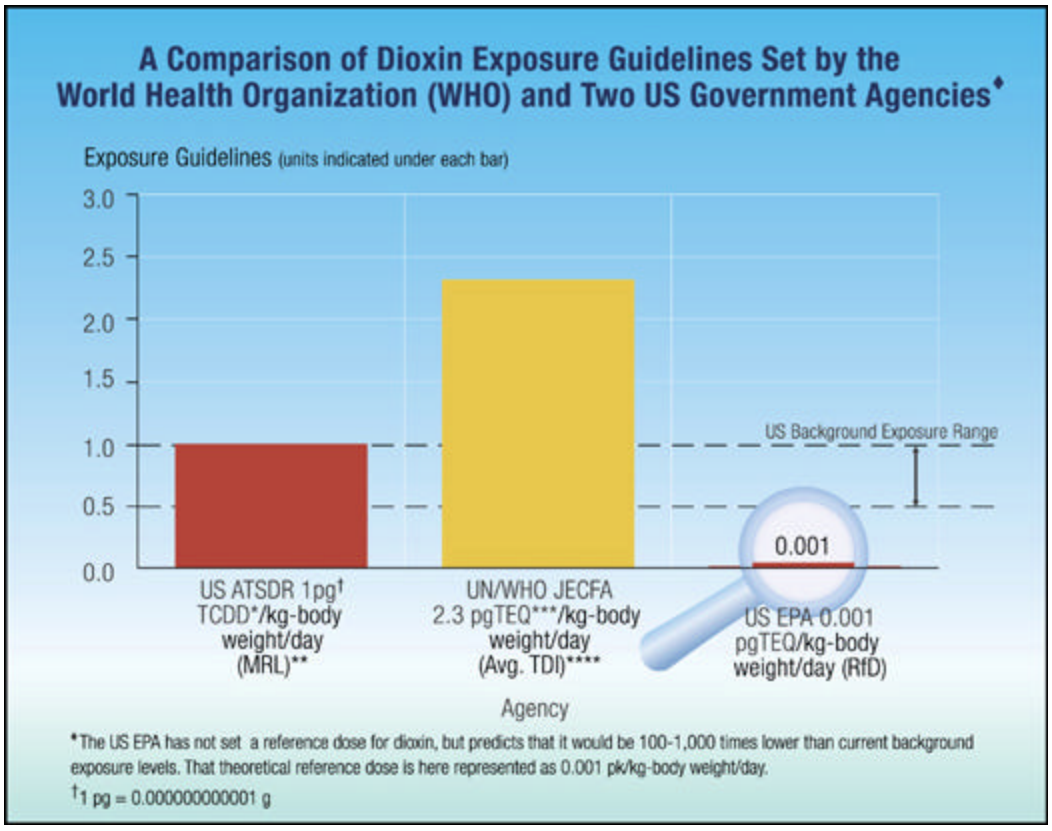
Agency	**US ATSDR**	**JECFA**	**EC SCF**	**US EPA**
Sensitive Non-cancer Endpoint Used	Behavioral effects of TCDD on monkeys	Reproductive effects on rodents	Cluster of endpoints in monkeys and rodents	None
Safety/Uncertainty Factor Used	90	9.6	9.6	-
Dioxin Exposure Guidelines (intake per day)	1.0 pg/kg-bw/day	2.3 pg/kg-bw/day	2 pg/kg-bw/day	[0.01-0.001 pg/kg-bw/day]

In a 2002 review, U.S. Agency for Toxic Substances and Disease Registry (ATSDR) scientists state, "The animal data suggest that the most sensitive endpoints of TCDD toxicity are immunotoxic, reproductive, and developmental," and that "…it is important to derive health-based guidance values for noncancer end points especially in accordance with emerging reports that reproductive and developmental end points are very sensitive to dioxins" (Pohl et al., 2002). The authors point to a world-wide convergence on the health assessment value being around 1 to 4 pg/kg/day.

Dioxin risk characterizations of the ATSDR, Joint United Nations Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) and European Commission Scientific Committee on Foods (EC SCF) are based on sensitive, non-cancer endpoints to which uncertainty factors are applied. The table above outlines dioxin exposure guidelines of these agencies and the data used to derive them. Thus, valid risk assessment procedures can be used to define dioxin exposure guidelines. Further, these guidelines, based on scientific, peer-reviewed animal studies and buffered with protective safety/uncertainty factors, are greater than or in the range of the

current median exposure background reported by the U.S. Environmental Protection Agency (EPA) of 0.5 to 1.0 pg/kg-bw/day.

TCDD exhibits the capacity to promote growth of cancer cells. In a long-term study of rats in which the incidence of liver tumors increased with TCDD exposure, the lowest observed effect level ("LOEL" = 10 ng/kg-bw/day) corresponded to a steady-state body level of 290 ng/kg-bw. According to JECFA (2001), in order for humans to attain a similar steady-state body level, they would have to intake 150 pg/kg-bw TCDD daily— between 150 and 300 times the current background exposure level. Clearly, TCDD cancer effects occur in laboratory animals at much higher exposure levels than those at which non-cancer effects occur. Basing exposure guidelines on sensitive, non-cancer endpoints, therefore incorporates protection from cancer effects.



In contrast to ATSDR, JECFA and the EC SCF, EPA has not set a reference dose for dioxin, but predicts it would be 100 to 1,000 times lower than current background exposure levels and values derived by those three entities. EPA

must explain why it will not consider a non-cancer endpoint in view of evidence, accepted by these three respected public health agencies, that dioxin non-cancer endpoints are more sensitive than cancer endpoints.

References:

European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Food (2001). Opinion of the SFC on the risk assessment of dioxins and dioxin-like PCBs in food. [Update based on new scientific information available since the adoption of the SCF opinion of 22nd November 2000. Adopted 30 May 2001.

Pohl, H.R., Hicks, H.E., Jones, D.E., Hansen, H., and De Rosa, C.T. (2002). Public Health Perspectives on Dioxin Risks: Two Decades of Evaluations. Human and Ecological Risk Assessment, 8, pp. 233-250.

US Agency for Toxic Substances and Disease Registry (1998). Toxicological profile for chlorinated dibenzo-p-dioxins. Prepared by Research Triangle Institute under contract no. 205-93-0606.

U.S. EPA (2000d). Science Advisory Board Review Draft: Exposure and human health reassessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds, Part III: Integrated summary and risk characterization for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds, September.

World Health Organization Food and Agriculture Organization of the United Nations (June, 2001). "Joint FAO/WHO Expert Committee on Food Additives, 57th Meeting, Rome, 5-14 June 2001, Summary and Conclusions."

Key Science Element #3: **The use of TEFs should be subjected to a more rigorous and current scientific review to assure the associated uncertainties are recognized and accounted for in their use in judging risk.**

Toxic Equivalency Factors (TEFs) were developed to facilitate risk assessment and regulatory control of dioxins and dioxin-like compounds, but their usefulness is severely limited. TEFs express the toxicities of dioxin-like compounds in terms of the toxicity of 2,3,7,8-TCDD[3] (TCDD), the most toxic and well-studied member of this group of compounds. However, TEF assignments are only order of magnitude estimates of the toxicities of the dioxin-like compounds relative to TCDD. Furthermore, the weight of science suggests that using TEFs incorporates a high degree of scientific uncertainty.

The validity of the TEF approach rests on several assumptions including:

- TCDD and the dioxin-like compounds act in a dose additive manner
- Each compound assigned a TEF elicits the same toxic endpoint—both cancer and non-cancer
- Dose-response curves for all compounds are parallel
- There is no effect from naturally occurring agonists (compounds that increase the toxicity of the mixture) or antagonists (compounds that decrease the toxicity of the mixture).

These sweeping assumptions in the TEF methodology render it inappropriate for predicting human health outcomes from exposure to dioxins at low background exposure levels. The U.S. Agency for Toxic Substances and Disease Registry has recognized the impact scientific uncertainties of the TEF approach can have on public health policies and setting appropriate risk levels (Pohl et al., 2002).

[3] The TEF of 2,3,7,8-TCDD is 1; all other TEFs are equal to or less than 1.

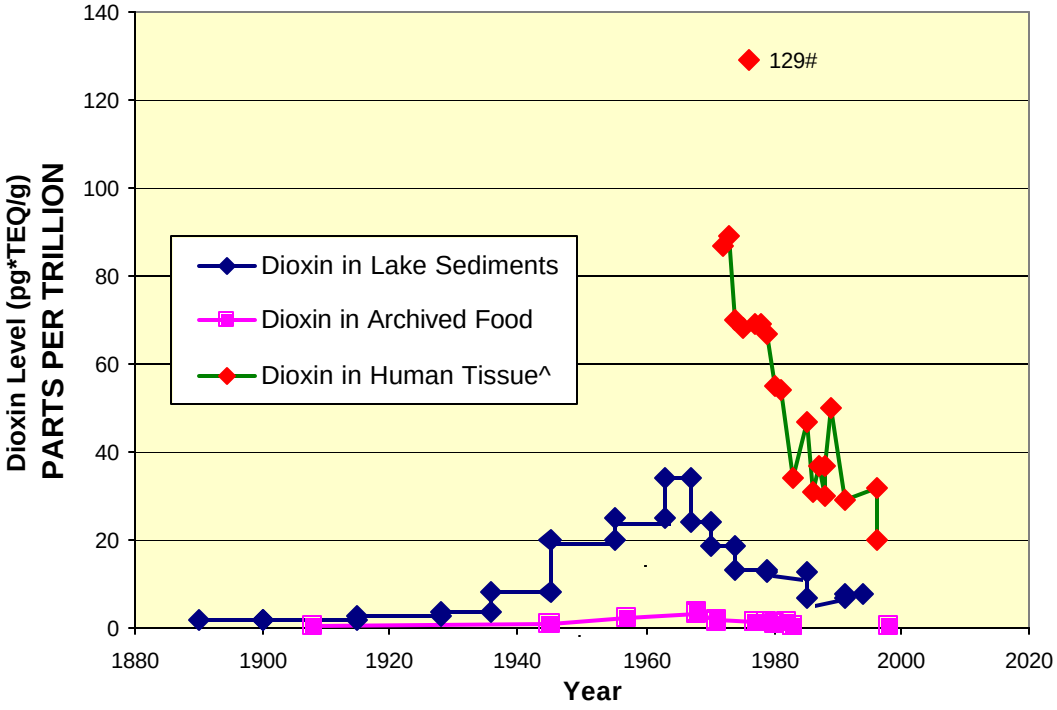
To summarize, the broad assumptions inherent in the calculation and use of TEFs create significant uncertainty in risk assessment. Analysis using empirical data is preferable to analysis that incorporates numerous policy decisions.

References:

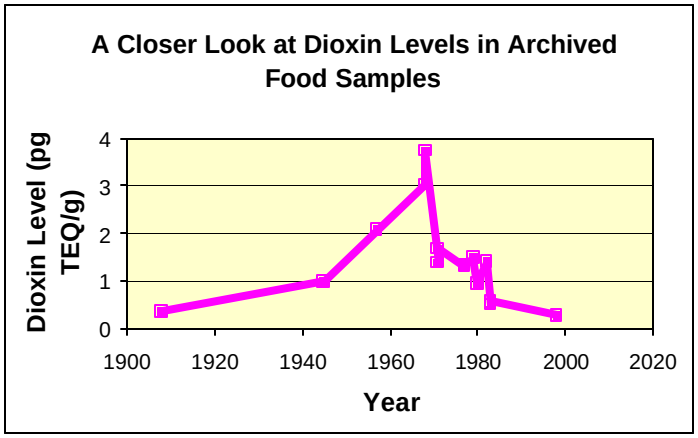
Pohl, H.R., Hicks, H.E., Jones, D.E., Hansen, H., and De Rosa, C.T. (2002). Public Health Perspectives on Dioxin Risks: Two Decades of Evaluations. Human and Ecological Risk Assessment, 8, pp. 233-250.

Key Science Element #4: **Exposure to dioxins via food and the environment continues to fall and more recent exposure level determinations need to be taken into account in the reassessment.**

TRENDS



Levels of dioxin in the environment and in human tissue are declining.

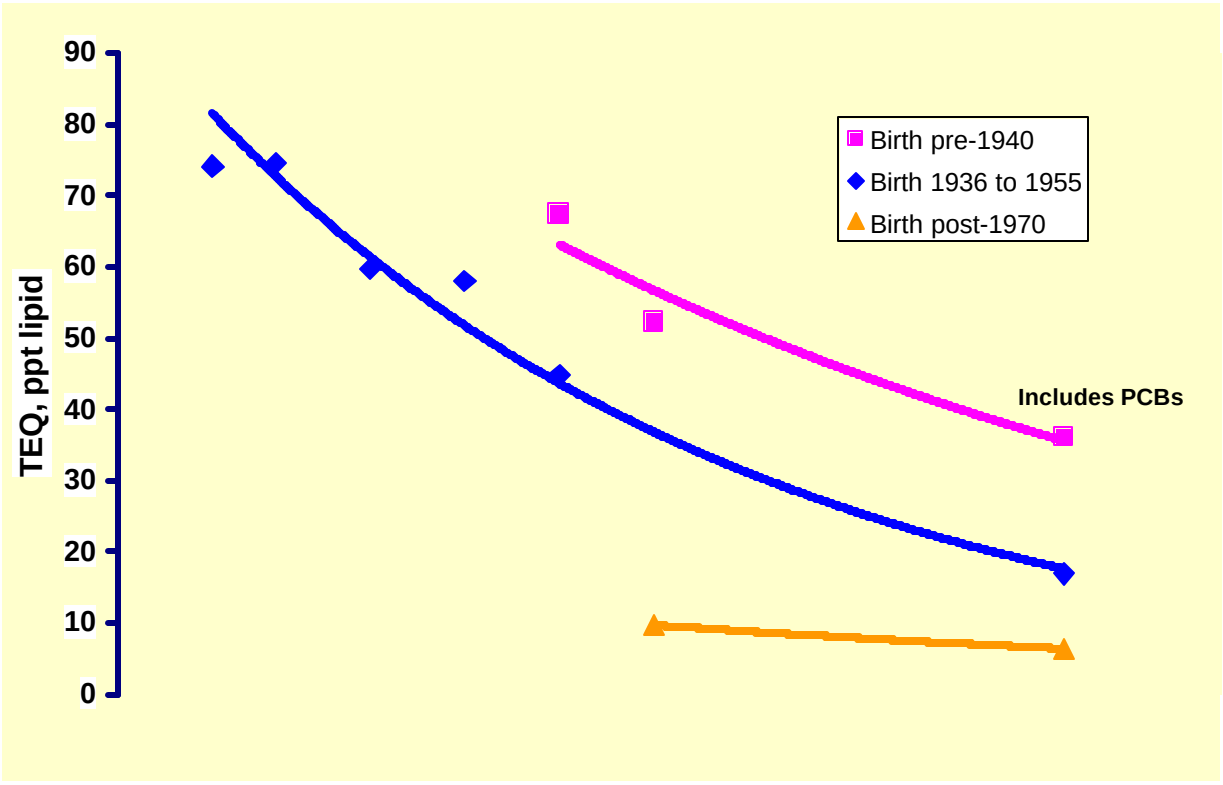


* 1 pg = 1 picogram (one-trillionth of a gram, 0.000000000001 g)
1 g = 1 gram (0.0022 lb.)
This value is treated here as an outlier.
^ Human tissue dioxin level data are virtually unavailable prior to the early 1970s

[These graphics are based on: Hagenmeier and Walczok (1996), Ferrario et al., (1998), Lorber (2002), Winters et al. (1998), Institute of Medicine of the National Academies Dioxin in the Food Supply report (2003).]

More on Trends:

Figure 1 Consistent with declining dioxin/furan levels in blood (upper plot), average dietary intakes of dioxin/furan have declined dramatically over the past 20 years (lower plot).



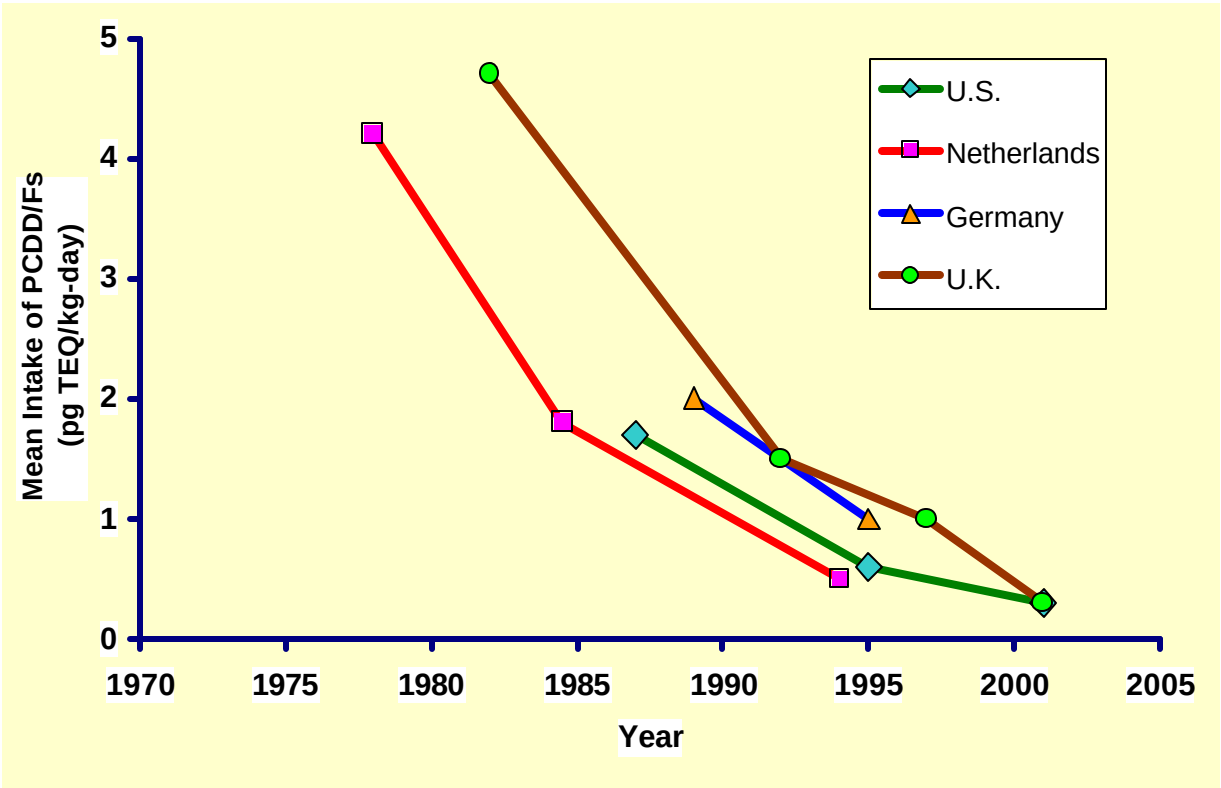
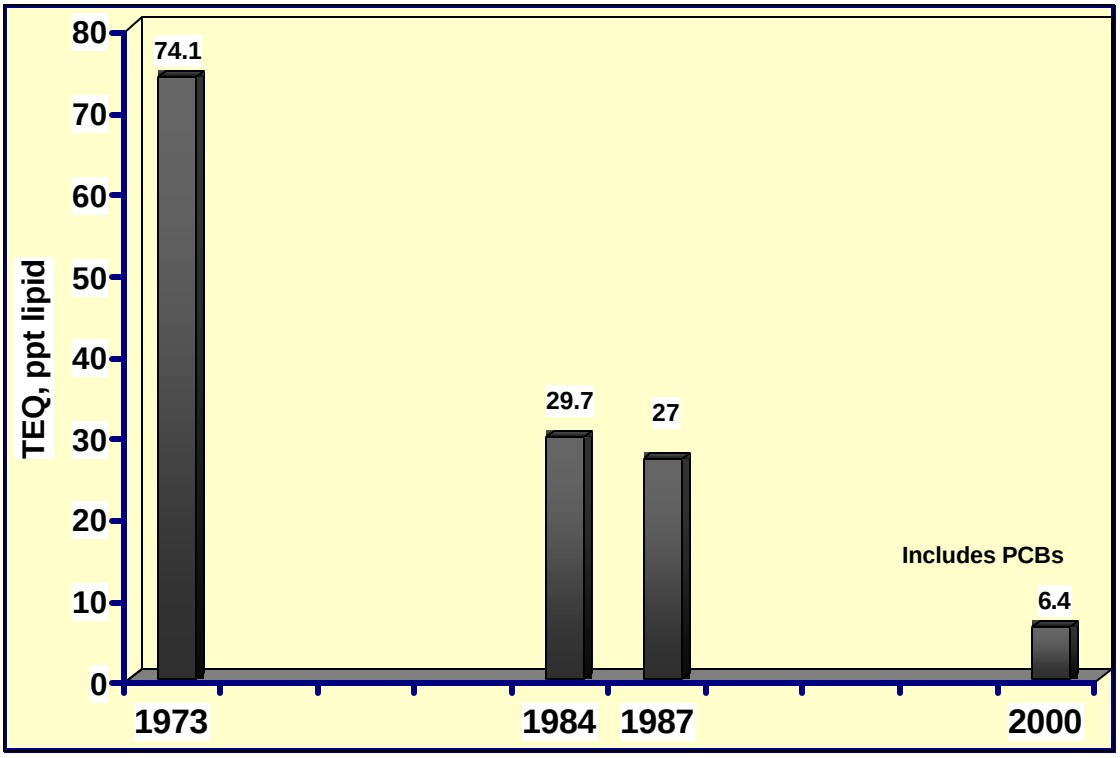


Figure 1 (upper plot) illustrates that dioxin/furan levels in blood are declining in people of all birth years, but the youngest of the population begin life with much lower levels of dioxin/furan than their parents or grandparents and will never experience the high body burdens accumulated by persons alive during the middle decades of the 1900s.

Consistent with declining body burden trends shown in the upper plot of Figure 1, the lower plot demonstrates that average dietary intakes of dioxins and furans have declined dramatically over the past 20 years in the U.S. and Western Europe.

Figure 2. Dioxin/Furan Blood Levels in People15-35 Years of Age Have Decreased Substantially Over Time



Since at least 1973, the average dioxin/furan level in people in the 15-35 year old range has declined significantly. The year 2000 data includes PCBs as well as dioxins and furans. Without PCBs, this data point would be even lower.

References for Figures 1 and 2 (on pages 15-16)

Serum lipid levels [Figure 1 (upper plot) and Figure 2]:

Graham, M., F.D. Hileman, R.G. Orth, J.M. Wendling, and J.D. Wilson 1986. Chlorocarbons in adipose tissue from a Missouri population. Chemosphere. 15:1595-1600.

Patterson, D.G., R. Canady, L.-Y. Wong, R. Lee, W. Turner, S. Caudill, L. Needham, and A. Henderson 2004. Age specific dioxin TEQ reference range. Organohalogen Compounds. 66:2878-2883.

Stanley, J.S., and J. Orban. Chlorinated dioxins and furans in the general U.S. population: NHATS FY87 Results. Final Report. Washington, D.C.: Office of Toxic Substances, U.S. Environmental Protection Agency; 1991. EPA-560/5-91-003.

Dietary intake [Figure 1 (lower plot)]:

Furst, P. 1997. Decline of human PCDD/F intake via food between 1989 and 1996. Organohalogen Compounds. 33:116-121.

Liem, A.K., P. Furst, and C. Rappe 2000. Exposure of populations to dioxins and related compounds. Food Addit Contam. 17(4):241-259.

United Kingdom Food Standards Agency 2003. Dioxins and dioxin-like PCBs in the UK diet: 2001 total diet study samples. Report 38/03.

United States Environmental Protection Agency (USEPA). Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin and Related Compounds. Draft Final. Washington, D.C.: National Center for Environmental Assessment, U.S. Environmental Protection Agency; 2000. EPA/600/P-00/001Be.

United States Food and Drug Administration. Total Diet Study Results. http://www.cfsan.fda.gov/~lrd/dioxee.html

The facts:

1. U.S. dioxin emissions from *man-made* sources have declined over 92% since 1987 due to a combination of effective government regulation and voluntary industry efforts [from 13,949 g*-TEQ/year in 1987 to 1,106 g-TEQ/year in 2002/2004].

2. Municipal solid waste incineration, historically the largest industrial source, has been reduced by over 99% since 1987 [from 8,877 g-TEQ/year ? 12 g-TEQ/year].

3. Backyard trash burning is currently the largest *man-made* source of dioxin emissions to the environment [~628 g-TEQ/year].

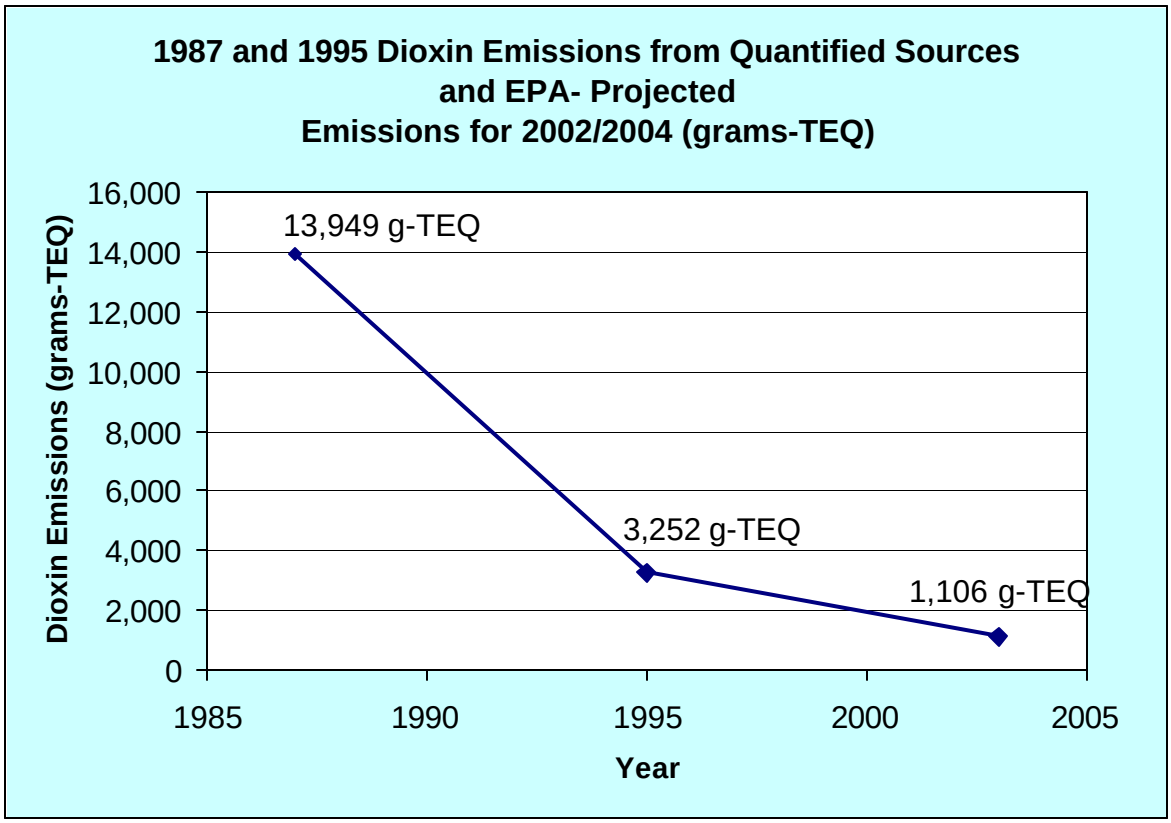
4. Forest fires are a major and *natural* source of dioxin [~1,000 g-TEQ/year].

5. Current levels of dioxin in our bodies are so low that a 2003 CDC study found dioxin levels in the blood of the average U.S. resident were below levels of detection.

*1 gram = 0.0000011 ton

Trends in Dioxin Levels in the Environment and in Humans

Total U.S. dioxin emissions from quantified man-made sources have declined over 92 percent since 1987 due to a combination of effective government regulation and voluntary industry efforts.



EPA estimates that *man-made dioxin emissions have been reduced by 92 percent since 1987* due to a successful combination of government regulations and voluntary industry efforts. Municipal solid waste incineration, historically the largest industrial source, has been reduced by over 99 percent since 1987. (For more information on trends in environmental levels of dioxin, go to:

http://www.cfsan.fda.gov/~lrd/dioxinqa.html

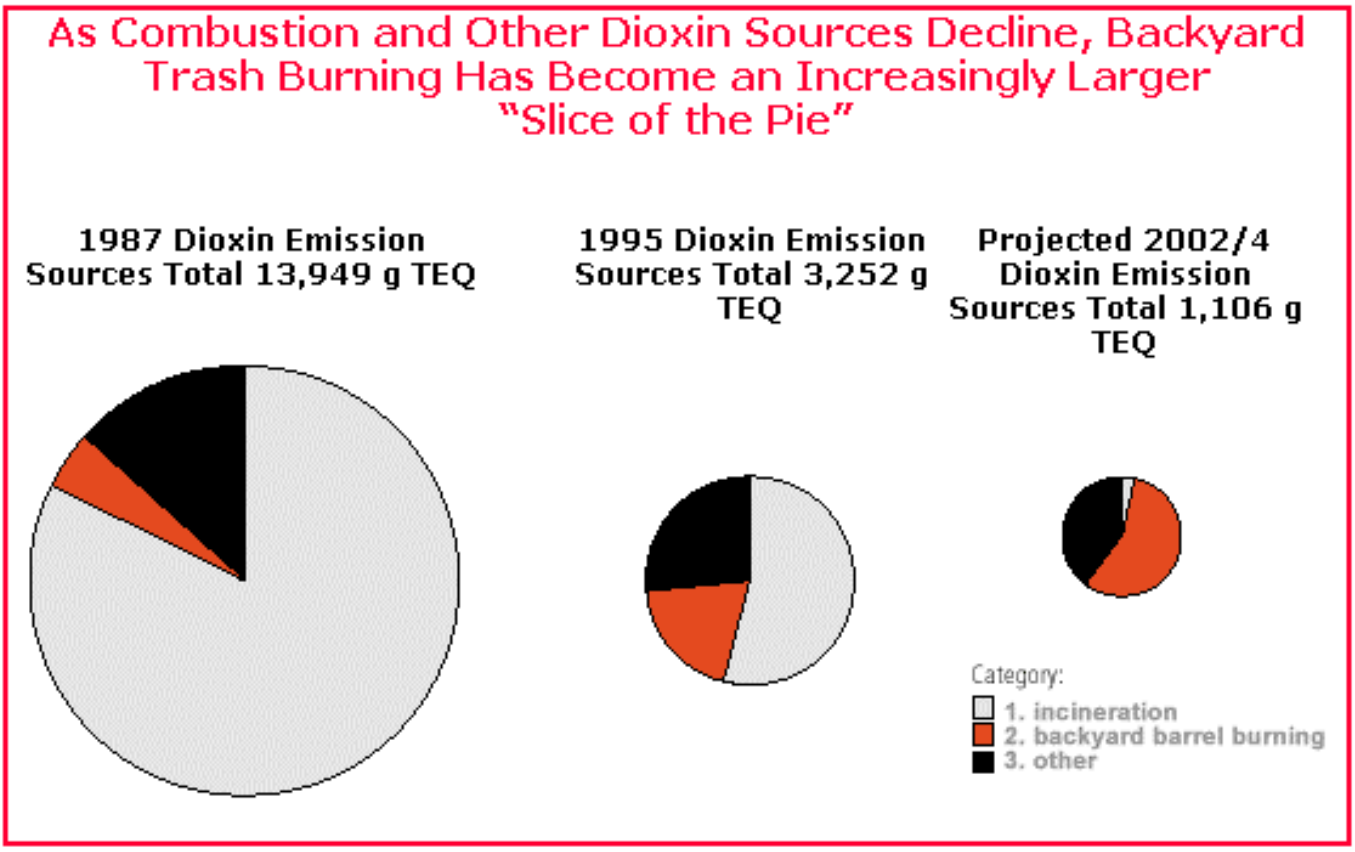
http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20797

www.dioxinfacts.org.)

Note: 1 gram = 0.0000011 ton

October, 2004

Backyard Trash Burning: The Largest Man-Made Source of Dioxin to the Environment

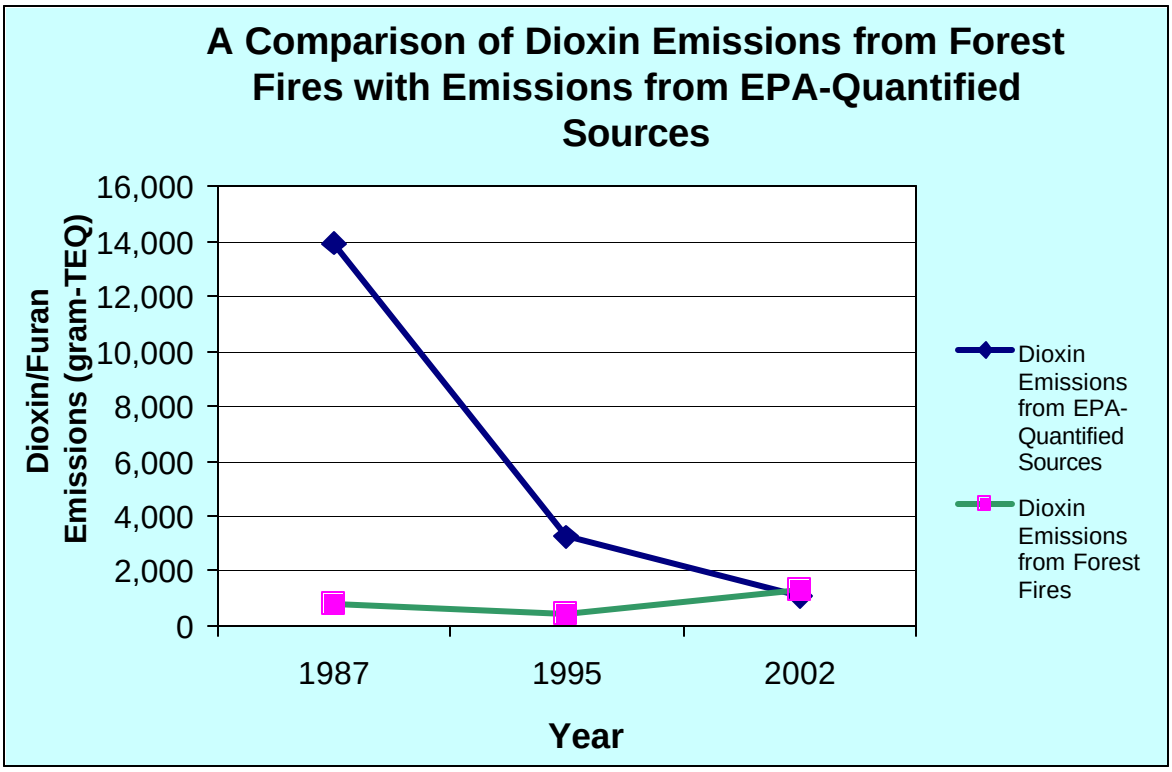


EPA data show backyard trash burning is currently the largest man-made source of dioxin emissions to the environment. A new EPA education campaign discourages this dangerous practice, which for some, has become a way of life in rural America. Currently, at least eight states have enacted full bans on backyard trash burning. (For more information on dioxin and backyard trash burning, go to:

http://www.epa.gov/epaoswer/non-hw/muncpl/backyard/pubs/st_local1.pdf

http://www.dioxinfacts.org/sources_trends/trash_burning.html.)

Forest Fires: A Major *Natural* Source of Dioxin



New research suggests that forest fires are a major and *natural* source of dioxin. In fact, in 2002, forest fires probably emitted nearly as much dioxin to the environment as did all other Environmental Protection Agency (EPA)-quantified sources *combined*. Dioxin emissions from industrial and commercial sources (*e.g.*, diesel trucks) have declined steadily over the past several decades. As emissions from these sources are further curtailed through regulation and technology, forest fires should continue to be viewed as a major source of dioxins to the environment. (For more information go to:

http://www.dioxinfacts.org/sources_trends/forest_fires.html.)

Note: 1 gram = 0.0000011 ton

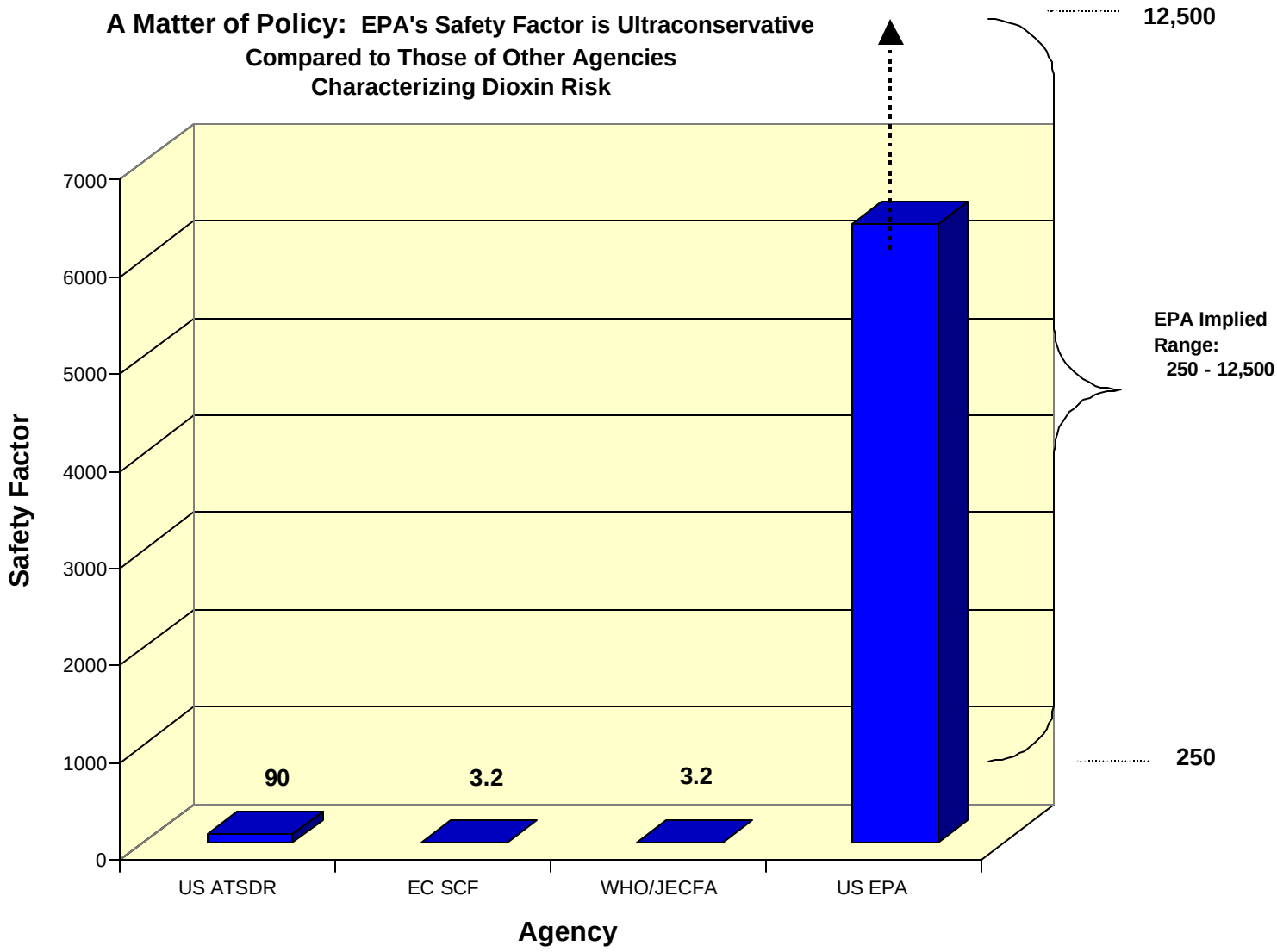
CDC Study Finds Dioxin Levels in Humans Below Levels of Detection

Current levels of dioxins in our bodies are so low that a recent U.S. Centers for Disease Control and Prevention (CDC) study found dioxin levels in the blood of the average U.S. resident were below levels of detection.

Recent CDC data confirm the fact that as environmental levels of dioxins fall, so do levels in the human body. The CDC's 2003 Second National Report on Human Exposure to Environmental Chemicals, reported levels of 116 compounds, including dioxins, in human blood. Dioxin levels in the average person sampled were found to be below the level of analytical detection set by CDC scientists. (For more information on dioxin and human biomonitoring, go to:

http://www.cdc.gov/exposurereport/

http://www.dioxinfacts.org/dioxin_health/cdc/Dioxin_TEQcombined.pdf.)


A Matter of Policy: EPA's Safety Factor is Ultraconservative
Compared to Those of Other Agencies
Characterizing Dioxin Risk
Safety Factor
7000
6000
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3000
2000
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US ATSDR
EC SCF
WHO/JECFA
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