Dioxin Risk: Are We Sure Yet?

As EPA's dioxin assessment undergoes public scrutiny, it is renewing debate on health risks and regulatory strategies.

On January 13, EPA will begin to sift through and assess hundreds of comments, studies, and opinions on one of the thorniest environmental science and health policy issues facing the United States: the risk dioxin and related compounds pose to humans. When the public comment period closes on that date, EPA's 2000-page draft dioxin risk assessment and risk characterization moves one step closer to becoming final, which is expected this September. More than three years in preparation, the reassessment provides the most comprehensive examination of dioxin-like compounds undertaken by the Agency. This *Environmental Science & Technology* Special Report presents an in-depth look at the report's major findings, the spectrum of opinion on the validity of EPA's assessment, and ways to control sources of dioxin.

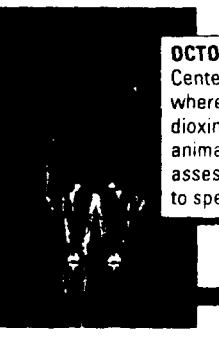
The latest assessment. Dioxin, one of the "most toxic chemicals regulated by EPA," according to EPA Assistant Administrator Lynn Goldman, has been the subject of a series of Agency assessments dating back to the early 1980s. This most recent evaluation began in 1991 because of several new studies as well as controversy about the health threat from dioxin-like compounds. One key piece of new information emerged from a 1990 meeting of scientists at the Banbury Center in New York, where a consensus was reached that dioxin-like compounds gain entry to cells by binding to a particular protein, the Ah receptor. Agreement on this mechanism and the results of studies of exposed workers led EPA to take another look at the compound.

Also driving the EPA reassessment were concerns by industry and others that the human health threat from dioxin had been overstated in risk assessments done in 1985 and 1988. This view, however, is refuted by the new assessment. EPA not only reaffirms the earlier view that dioxin is a probable human carcinogen, but also finds that noncancer health effects are greater than was previously thought. The report describes a complex and only partially understood interplay among dioxin-like compounds, hormones, and other modulators of cell growth and differentiation. In shoring up past scientific views on cancer risk from dioxin, the assessment also found that the upper bound risk estimates for cancer in the general population exposed to dioxin may be as high as one in ten thousand to one in a thousand.

When the risk reassessment was first an-

Milestones in EPA's Assessment of Dioxin

1985: EPA issues first dioxin risk assessment, focused primarily on cancer and based largely on animal studies. Dioxin classified as a probable, highly potent human carcinogen.



OCTOBER: Scientific meeting at Banbury Center, Cold Springs Harbor Laboratory, where experts agree that human effects from dioxin can be predicted from effects in animals and the development of risk assessment model based on dioxin binding to specific cellular receptor is needed.

1988: EPA issues draft revised assessment, suggesting dioxin less potent. General agreement that current procedures inadequate to assess dioxin's human health risks. Later in year, EPA Science Advisory Board finds no scientific basis for revising dioxin potency estimates but recommends new model be developed for assessing risk.

APRIL: EPA administrator directsAgency to beg - major reassessment of risks from dioxin. Tasks include development of biologically based dose-response model, lab research to support study, update of health and exposure assessment, and research to characterize risk in aquatic ecosystems.

NOVEMBER: First of two public meetings convened by EPA to receive comments and report progress

0013-936X/95/0929-24A$09.00/0

nounced by then-EPA Administrator William Reilly in 1991, it was expected to be completed in less than two years. However, the process took considerably longer at least in part because EPA brought in outside scientists to review each risk assessment chapter as it was being developed. Some 100 scientists inside and outside EPA were involved in the review. This unprecedented action has been widely praised.

Noncancer effects. Most significant in this analysis is the heightened concern about noncancer effects in humans, including disruption of the endocrine, reproductive, and immune systems, as well as dioxin's impact on the developing fetus, which may occur in some cases at or near background levels The draft points to studies showing decreased sperm count in men, higher probability of endometriosis in women, weakened immune systems, and other health problems. Certain highly exposed subpopulations may already be experiencing some of these effects, according to the new assessment.

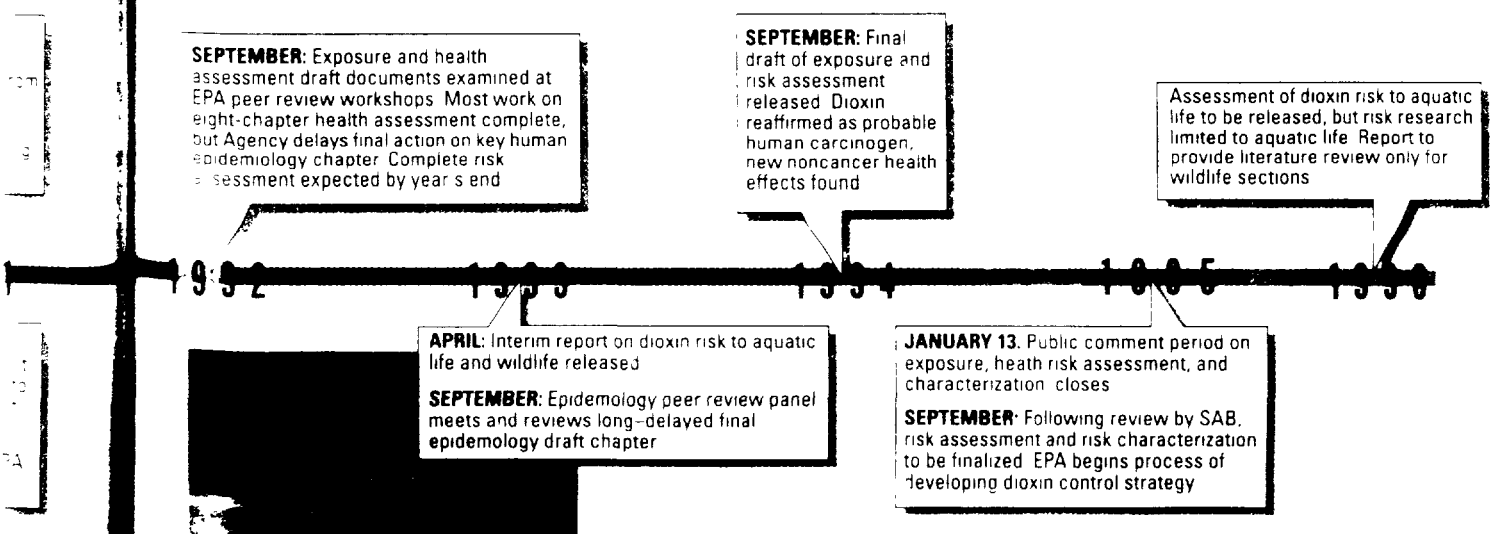
The risk assessment document presents new information on exposure as well as health effects (see p. 26A). The volume on estimating exposure to dioxin-like compounds in the United States represents the most comprehensive effort undertaken to identify sources and the major routes of exposure. Airborne deposition appears to be the most prevalent means of transport. The compound then makes its way into the human food chain through ingestion of contaminated plants by animals and bioaccumulation of dioxin in fatty tissue Human exposure through consumption of beef, dairy products, fish, and other food products can result in dose rates that are several orders of magnitude greater than exposure through inhalation, which had been considered the primary route of general exposure in previous assessments.

Four primary sources are identified: combustion and incineration, chemical manufacturing, industrial municipal processes, and reservoir sources in which dioxin may be recirculated throughout the environment once it is generated. Although incinerators appear to be the greatest dioxin contributor, the report notes that several sectors, such as the chemical manufacturing industry, may be large generators but have not been characterized because of insufficient data.

Call for action. Environmental groups generally support EPA's assessment but call for immediate regulatory action to limit sources of dioxin (see p. 29A) Agency officials, however, say they will not propose regulatory changes based on the results of the risk assessment until after the report is finalized this fall. Still, EPA is proposing new regulations to limit dioxin emissions from incinerators (see p. 33A).

Industry groups have voiced criticism of the draft report as well as the proposed incinerator regulations (see p. 31A). Dioxin is created inadvertently by a host of industrial activities in which chlorine-based compounds are exposed to high heat in the presence of organic material. Industrial processes identified in the report include waste incineration, chemical manufacturing, chlorine bleaching of pulp and paper, and smelting.

As part of the final draft review, EPA has asked scientists, industries, state and local governments, and others to provide new data on dioxin. Over the next few months EPA will assess these comments, prepare a final version of the risk document, and forward it to the EPA Science Advisory Board for review. When the assessment is finalized, it will be the first EPA dioxin risk assessment that has advanced beyond the draft stage in a decade —JEFF JOHNSON



EPA's Dioxin Reassessment

Highlights from EPA's three-year effort to document sources, exposures, and impact on health

Following are excerpts from EPA's health assessment (1) and exposure estimates (2, 3) of dioxin (TCDD) and related compounds, which include chlorinated dibenzodioxins (CDDs), chlorinated dibenzofurans (CDFs), and polychlorinated biphenyls (PCBs) thought to have dioxin-like toxicity. These draft documents do not represent Agency policy. EPA's reference citations are not included; see documents listed in References for this information. —Editor

Based on all of the data reviewed in this reassessment and scientific inference, a picture emerges of TCDD and related compounds as potent toxicants in animals with the *potential* to produce a spectrum of effects. Some of these effects may be occurring in humans at very low levels and some may be resulting in adverse impacts on human health.

The potency and fundamental level at which these compounds act on biological systems are analogous to several well-studied hormones. Dioxin and related compounds have the ability to alter the pattern of growth and differentiation of a number of cellular targets by initiating a series of biochemical and biological events resulting in the potential for a spectrum of responses in animals and humans. Despite this potential, there is currently no clear indication of increased disease in the general population attributable to dioxin-like compounds. The lack of a clear indication of disease in the general population should not be considered strong evidence for no effect of exposure to dioxin-like compounds. Rather, lack of a clear indication of disease may be a result of the inability of our current data and scientific tools to directly detect effects at these levels of human exposure (*1*, pp. 9-87, 9-88).

The presence of dioxin-like compounds in the environment has occurred primarily as a result of anthropogenic practices.

Ancient human tissue sampling shows much lower CDD/F levels than found today. Studies of sediment cores in lakes near industrial centers of the United States have shown that dioxins and furans were quite low until about 1920. These studies show increases in CDD/F concentrations beginning in the 1920s and continuing until about 1970. Declining concentrations have been measured since this time. These trends cannot be explained by changes in natural processes and have been shown to correspond to chlorophenol production trends. On this basis, it appears that the presence of dioxin-like compounds in the environment occurs primarily as a result of anthropogenic practices (*2*, p. 12).

The major identified sources of environmental release have been grouped into four major types for the purposes of this report: industrial/municipal processes, chemical manufacturing/processing sources, combustion and incineration sources, and reservoir sources (*3*, pp. 3-2, 3-3).

This assessment proposes the hypothesis that the primary mechanism by which dioxin-like compounds enter the terrestrial food chain is via atmospheric deposition.

Deposition can occur directly onto plant surfaces or onto soil. Soil deposits can enter the food chain via direct ingestion (i.e., earthworms, fur preening by burrowing animals, incidental ingestion by grazing animals, etc.). CDD/F in soil can become available to plants by volatilization and vapor absorption or particle resuspension and adherence to plant surfaces. In addition, CDD/F in soil can adsorb directly to underground portions of plants, but uptake from soil via the roots into above ground portions of plants is thought to be insignificant (*2*, p. 31).

The major route of human exposure is through ingestion of foods containing minute quantities of dioxin-like compounds (*1*, p. 9-14).

Dietary intake is generally recognized as the primary source of human exposure to CDD/Fs. Several studies have estimated that over 90 percent of

the average daily exposure to CDD/Fs are derived from foods. CDD/Fs in fatty foods such as dairy, fish, and meat products are believed to be the major contributors to dietary exposures (3, pp. 4-22, 4-23).

The published data on measured levels of CDDs, CDFs, and dioxin-like compounds in U.S. food products have generally come from studies of a specific food product(s) in a specific location(s) rather than from large survey studies designed to allow estimation of daily intake of the chemicals for a population (3, p. 4-25).

The scientific community has identified and described a series of common biological steps that are necessary for most if not all of the observed effects of dioxin and related compounds in vertebrates, including humans.

Binding of dioxin-like compounds to a cellular protein called the "Ah receptor" represents the first step in a series of events attributable to exposure to dioxin-like compounds, including biochemical, cellular, and tissue-level changes in normal biological processes. Binding to the Ah receptor appears to be necessary for all well-studied effects of dioxin but is not sufficient, in and of itself, to elicit these responses. This reassessment concludes that the effects elicited by exposure to 2,3,7,8-TCDD are shared by other chemicals that have a similar structure and Ah receptor-binding characteristics. Consequently, the biological system responds to the cumulative exposure of Ah receptor-mediated chemicals rather than to the exposure to any single dioxin-like compound (1, p. 9-78).

The reliability of using animal data to estimate human hazard and risk has often been questioned for this class of compounds. Although human data are limited, evidence suggests that animal models are appropriate for estimating human risk if all available data are considered. Humans have a fully functional Ah receptor and both in vivo and in vitro studies demonstrate comparability of biochemical responses in humans and animals (1, p. 9-36).

There is adequate evidence based on all available information to support the inference that humans are likely to respond with a broad spectrum of effects from exposure to dioxin and related compounds if exposures are high enough (1, 9-79).

The potential for dioxins and related compounds to cause reproductive and developmental toxicity in animals has been recognized for many years. Recent laboratory studies have suggested that altered development may be among the most sensitive TCDD end points in laboratory animal systems although the likelihood and level of response in humans are much less clear. . .

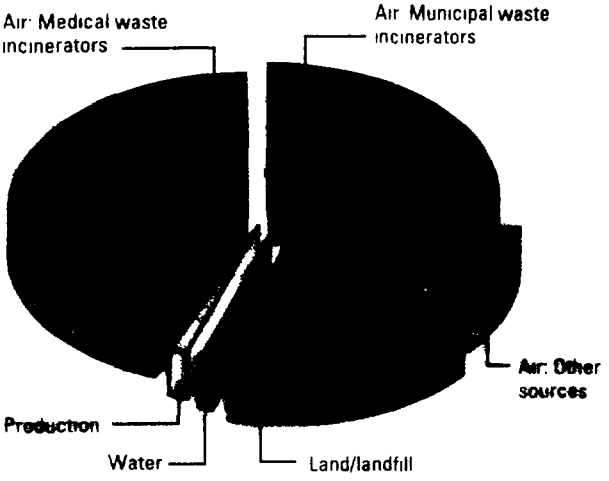
Of particular interest to the risk assessment process is the fact that a wide variety of developmental events, crossing three vertebrate classes and several species within each class, can be perturbed, suggesting that dioxin has the potential to disrupt a large number of critical developmental events at specific developmental stages (1, pp. 9-44, 9-45).

With respect to male and female reproductive end points, there are clear effects following dioxin exposure of the adult animal. Such reproductive effects generally occur at TCDD body burdens that are higher than those required to cause the more sensitive developmental end points (1, p. 9-47).

Observations described in this assessment suggest a continuum of response to exposure to dioxin-like chemicals. By a continuum of response we suggest that as dose increases, the probability of occurrence of individual effects increases and the severity of collective effects increases. This continuum provides a basis for inferring a relationship between some early events that are not necessarily considered to be adverse effects with later events that are adverse effects. . . This inference may be the most contentious of all (1, pp. 9-73, 9-74).

U.S. sources of dioxin-like compounds

EPA's draft reassessment presents the first compilation of nationwide CDD/CDF emission estimates. It shows that emissions from incinerators to the atmosphere are the dominant dioxin source in the United States. These "best guess" values are, according to EPA, "quite uncertain since the nationwide approximations were derived by extrapolating only a few facility tests" (2). No estimates were made of some potential sources, such as chemical manufacturing, because of the lack of test data.



Average background exposure leads to body burdens in the human population that average 40–60 pg TEQ [TCDD equivalents]/g lipid (40–60 ppt) when all dioxins, furans, and PCBs are included.

The term "background" exposure has been used throughout this reassessment to describe exposure of the general population that is not exposed to readily identifiable point sources of dioxin-like compounds. Data on human tissue levels suggest that body burden levels among industrialized nations are reasonably similar. These data can also be used to estimate background exposure through the use of pharmacokinetic models.

Using this approach, exposure levels to 2,3,7,8-TCDD in industrialized nations are estimated to be about 0.3–0.6 pg TCDD/kg body weight/day. Estimates based on the contribution of dioxin-like PCBs raise the total to 3–6 pg TEQ/kg body weight/day. This range is used throughout this characterization as an estimate of average background exposure to dioxin-like CDDs, CDFs, and PCBs.

High-end estimates of body burden of individuals in the general population (approximately the top

Health effects in humans and animals

The exposure levels at which health effects from dioxin-like compounds are observed vary widely among species. A sampling of the studies presented in the EPA dioxin health assessment indicates that some health effects are observed at estimated body burden levels close to the average human "background" body burden level.

Effect	Species	Estimated body burden of dioxin (ng/kg)
"Background" level	*Human*	*9*
"Causally associated" with dioxin exposure		
Chloracne	Human	45–3000
	Monkey	1000
	Rabbit	220
	Mouse	14,000
"Associated" with dioxin exposure		
Cancer	Human	109–7000
	Hamster	500
	Mouse	1000
Decreased testosterone	Human	83
Decreased testis size	Human	14
	Rat	10,200
Altered glucose tolerance	Human	14–110
"Low-dose effects" in animals		
Endometriosis	Monkey	54
Decreased sperm count	Rat	64
Decreased offspring viability	Rhesus monkey	270
Enhanced viral susceptibility	Mouse	7

Source: Reference 1, pp 9-55–9-65

10% of the general population) may be greater than three times higher (*1*, pp. 9-77, 9-78).

The margin of exposure between background levels and levels where effects are detectable in humans in terms of TEQs is considerably smaller than previously estimated (*1*, 9-81).

In TCDD-exposed men, subtle changes in biochemistry and physiology, such as enzyme induction, altered levels of circulating reproductive hormones, or reduced glucose tolerance, have been detected in a limited number of available studies. These findings, coupled with knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism and developmental and/or reproductive biology. . .

Subtle changes in biochemistry and physiology are seen with TCDD exposures at or just several fold above average [body burden] TEQ levels. Since exposures within the general population are thought to be log-normally distributed, individuals at the high end of the general population range (with body burdens estimated to be three, and perhaps as high as seven, times higher than the average) may be experiencing some of these effects.

The likelihood that noncancer effects may be occurring in the human population at environmental exposure levels is often evaluated using a margin of exposure [MOE] approach. A MOE is calculated by dividing the human-equivalent animal lowest observed adverse effect level with the human exposure level. MOEs in the range of 100 to 1,000 are generally considered adequate to rule out the likelihood of significant effects occurring in humans based on sensitive animal responses. The average levels of intake of dioxin-like compounds in terms of TEQs in humans described above would be well within a factor of 100 of levels representing lowest observed adverse effect levels in laboratory animals exposed to TCDD or TCDD equivalents. For several of the effects noted in animals, a MOE of less than a factor of 10, based on intake levels or body burdens, is likely to exist.

. . . [It is] highly unlikely that a margin of exposure of 100 or more currently exists for these effects at background intake levels, at least for some members of the human population (*1*, pp. 9-81–9-83).

Dioxin and related compounds are likely to present a cancer hazard to humans (*1*, p. 9-85).

Since the last EPA review of the human data base relating to the carcinogenicity of TCDD and related compounds in 1988, several new follow-up mortality studies have been completed. . . . Although uncertainty remains in interpreting these studies because not all potential confounders have been ruled out and coincident exposures to other carcinogens is likely, all provide support for an association between exposure to dioxin and related compounds and increased cancer mortality (*1*, p. 9-39).

While major uncertainties remain, efforts of this reassessment to bring more data into the valuation of cancer potency have resulted in a risk-specific dose estimate (1×10^{-6} risk or one additional cancer in one million exposed) of approximately 0.01 pg TEQ/kg body weight/day. This risk-specific dose estimate represents a plausible upper bound on risk based on the evaluation of animal and human data. . .

With regard to average intake, humans are currently exposed to background levels of dioxin-like compounds on the order of 3–6 pg TEQ/kg body weight/day, including dioxin-like PCBs. This is more than 500-fold higher than the EPA's 1985 risk-specific dose associated with a plausible upper-bound, one in a million risk of 0.006 pg TEQ/kg body weight/day . Plausible upper-bound risk estimates for general population exposures to dioxin and related compounds, therefore, may be as high as 10^{-2} to 10^{-3} (one in ten thousand to one in a thousand) (*1*, pp. 9-85, 9-86).

References

1. U.S. Environmental Protection Agency. *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*. Vol. III external review draft. Office of Health and Environmental Assessment. Office of Research and Development. U.S. Government Printing Office. Washington, DC. August 1994. EPA 600/BP-92/001C.
2. U.S. Environmental Protection Agency. *Estimating Exposure to Dioxin-Like Compounds. Vol. I: Executive Summary*: external review draft. Office of Health and Environmental Assessment. Office of Research and Development. U.S. Government Printing Office. Washington, DC. June 1994. EPA/600/6-88/005Ca.
3. U.S. Environmental Protection Agency. *Estimating Exposure to Dioxin-Like Compounds. Vol. II: Properties, Sources, Occurrence and Background Exposures*: external review draft. Office of Health and Environmental Assessment. Office of Research and Development. U.S. Government Printing Office. Washington, DC. June 1994. EPA/600/6-88/005Cb.

EPA on the Right Track

RICHARD CLAPP
PETER deFUR
ELLEN SILBERGELD
PETER WASHBURN

The public finally has access to the full official text of the current dioxin reassessment. In announcing the release, EPA declared that the present assessment differs from other assessments for procedural as well as substantive reasons. The document produced by EPA and independent scientists is not, however, what industry expected when it pushed the Agency to undertake the reassessment. Instead of declaring the risks lower, the draft report finds the risks are greater than previously thought. The environmental community is satisfied that EPA is at last on the right track.

EPA recognizes that the policy implications of this reassessment may require new implementation strategies. We believe EPA is obligated to set a national policy consistent with the threat—one that identifies and eliminates all sources of or exposures to dioxin-like compounds.

The process EPA used for this reassessment was, wisely, akin to scientific peer review. From the outset, EPA announced that outside scientists would be integrally involved in writing the documents to summarize the current knowledge of the dioxin-related compounds. In the past, the perception had been that EPA completed such assessments behind closed doors. This process, albeit slow, was substantially enhanced over past ones, and the results are correspondingly improved, despite missed deadlines.

A comprehensive analysis

The scope of the EPA dioxin reassessment includes not just 2,3,7,8-TCDD but all dioxin-like compounds. This approach is the only one consistent with research showing that a number of congeners act through the same receptor mechanism within cells (*1, 2*). The subsequent quantitative ranking of chemicals according to their ability to act via the same receptor mechanism yields a more complete analysis of the total load of dioxin-like compounds in the environment and living systems.

EPA also expanded the end points to include wildlife and aquatic life. Past assessments of dioxin were never intended as more than human health assessments. Although the current effort produced an important summary of wildlife and aquatic life effects, that part was never completed as originally envisioned. Still, the limited report on wildlife and aquatic life (*3*) clearly indicates that these animals are as sensitive as any others to the dioxin-like compounds.

The draft report finds the risks are greater than previously thought.

Although EPA had previously addressed some of the noncancer health effects of dioxin, these effects had not been given the same level of scrutiny as cancer. But the Banbury conference pointed to the effectiveness of low doses in provoking developmental changes that have dramatic consequences. Now, the reassessment acknowledges that these noncancer end points are cued via endocrine systems altered by dioxin-like compounds, and the most sensitive biological system may be the developing fetus.

Exposures and sources. The question of how much dioxin is released into the environment now and how much remains from past releases was originally considered fairly straightforward. But when the reassessment was first publicly reviewed in September 1992, comments indicated that a more complete source inventory was needed. Consequently, the current version contains a more complete summary of sources, exposure pathways, and concentrations in various media. According to the report, the greatest sources are incinerators. Also, aquatic discharges may result in important exposures through the food chain. But a large fraction is unassigned to

specific sources, recirculation of existing contamination may be substantial.

The information is not complete, particularly regarding concentrations in all animal tissues. However, the report shows that the level and extent of contamination are greater than previously supposed. Dioxin-like compounds are widespread in soils, sediments, and animal tissues. In food, fish has the highest level of dioxin-like compounds (average 0.6–1.0 pg/g); beef is nearly half that; pork, chicken, and dairy products have only slightly lower concentrations than beef. For comparison, health advisories issued by state agencies frequently caution against the consumption of fish with 1–2 pg/g or more total dioxin-like compounds, based on toxic equivalents.

Human health. Earlier EPA health assessments of dioxin, using the one compound, were based on two-year cancer bioassays. The seminal piece of work was the research by Kociba (4) on rat liver cancer that yielded an estimated cancer potency of dioxin (2,3,7,8-TCDD specifically) higher than ever determined for any compound. EPA used the standard assumptions of linearity of the dose–response function and lack of an effects threshold at low doses. But even at the outset of the current reassessment, it was clear that both of these assumptions were being tested. These assumptions, after all, drove the calculation of the cancer potency and subsequent dose-specific risk estimates.

No response threshold

The acceptance of the Ah receptor mechanism led to the suggestion that the response was not linear at low doses and that a response threshold occurred at low levels. But a focused examination of the low-dose–response function refuted both notions (5). This confirmation of the nonthreshold and dose–response linearity assumptions reinforced EPA's earlier health assessments. Consequently, EPA had to accept that dioxin is fully as carcinogenic as originally considered. The recent publication of human epidemiological data from accidental and occupational exposures to dioxin provided further evidence of the carcinogenicity. Little doubt can now exist that dioxin is a human carcinogen.

Even before the reassessment began, research pointed to the importance of noncancer effects of the dioxin-like compounds. A wealth of data existed, in fact, on noncancer effects, but these were considered secondary to cancer. But the elegant work carried out in the lab of Peterson (6) changed that assumption forever. Mably et al. showed that administration of a single dose of dioxin to a pregnant rat can affect the development of reproductive function in male offspring.

Mechanism of action. The central point of the Banbury conference was the molecular level of action for dioxin and related compounds. Researchers recognized that dioxin functions at the molecular level in much the same manner as steroid hormones, via binding to an intracellular protein receptor. This realization led to the recognition that an entire group of compounds capable of binding to this same receptor was competent to provoke the same suite of responses as 2,3,7,8-TCDD.

The receptor-based mechanism of action affected the scientific reassessment more than any other single aspect of the larger issue. The receptor mechanism prompted EPA to undertake the effort in the belief that a better model would emerge from understanding the molecular basis. The molecular pathway of receptor binding led to the inclusion of additional chemicals that follow this path and the inference that these dioxin-like compounds can be quantitatively compared with 2,3,7,8-TCDD (the toxic equivalency, or TEQ, concept). And the fact that the receptor mechanism is found in humans, experimental laboratory animals, and wildlife provides conclusive support for the use of animal data.

Eliminate sources and exposures

Problems with the use of science in environmental regulation and policy making often revolve around determining when the Agency has enough data to stop studying and start fixing the problem. EPA has faced that question for the past 10 years, and until now has determined that the evidence supported action to protect against cancer in humans. Now EPA faces increasing data on low-dose effects of, and widespread exposures to, all dioxin-like compounds.

It is clear EPA must adopt a management approach similar to that for lead and at least attempt to identify and eliminate all the sources. The lead model will serve EPA well in initiating a control strategy. With lead, EPA recognized that the entire population was exposed through multiple sources, with health consequences at low-dose exposures. The source-by-source control strategy failed to protect human health or the environment. Instead, all exposures had to be controlled or eliminated and sources treated similarly. The success of that approach has been the decline in blood lead levels reported in 1994.

We believe there is no alternative but to take a similar approach and eliminate sources and exposures. In the case of the dioxin-like compounds, however, the lead model must serve as only the start. EPA must rigorously eliminate sources as well as exposures, recognizing that each exposure threatens human health and the environment.

References

1. "Biological Basis for Risk Assessment of Dioxins and Related Compounds", Gallo, M. A., Scheuplein, R. J., van der Heijden, K. A., Eds., Banbury Report 35; Cold Spring Harbor Laboratory Press: New York, 1991.
2. Ahlborg, U. G. et al. *Eur. J. Pharmacol. Environ. Toxicol. Pharmacol.* **1992**, *228*, 179–99.
3. "Interim Report on Data and Methods for Assessment of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Risks to Aquatic Life and Associated Wildlife", U.S. Environmental Protection Agency: Washington, DC, 1993; EPA/600/R-93/055.
4. Kociba, R. J. et al. *Toxicol. Appl. Pharmacol.* **1978**, *46*, 279–303.
5. Portier, C. et al. *Fundam. Appl. Toxicol.* **1993**, *20*, 48–56.
6. Mably, T. A., Moore, R. W., Peterson, R. E. *Toxicol. Appl. Pharmacol.* **1992**, *114*, 188–226.

Richard Clapp is an epidemiologist and professor at Boston University. Peter deFur is a senior scientist for the Environmental Defense Fund. Ellen Silbergeld is a senior scientist for the Environmental Defense Fund and a member of the Executive Committee of EPA's Science Advisory Board. Peter Washburn is a staff scientist with the Natural Resources Council of Maine.

EPA Assessment Not Justified

ENVIRON DIOXIN RISK
CHARACTERIZATION EXPERT PANEL

EPA has concluded that adverse impacts on human health may occur from exposure to dioxin-like compounds at or within an order of magnitude of current background body burdens. We do not believe there is sufficient scientific evidence to support this alarming conclusion. Dioxin exposure clearly causes a variety of toxicologic effects in laboratory animals, and scientists generally agree that most of these effects are mediated through the Ah receptor. However, the exposures estimated to give rise to human background body burdens are far smaller than those known to cause toxicity. The pivotal issue is thus whether adverse human health effects can reasonably be expected to occur at or near current background body burdens.

EPA has equated acute and chronic exposure patterns on the basis of projected body burdens even though the corresponding daily doses can be orders of magnitude apart. Because adipose tissue, the major storage site for dioxin, equilibrates slowly, acute dioxin administration will produce higher peak concentrations in serum and target organs than will administration of the same total dose in small daily increments. Use of body burden as a measure of exposure is thus misleading.

Additivity questioned

Compounds that bind to the Ah receptor include dioxin-like polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) that are present in vastly greater concentrations than 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) itself. In fact, most of the background body burden in humans is caused by these other chemicals. Use of toxic equivalency factors (TEFs) implies that all of these compounds act in an additive manner. However, this hypothesis is contradicted by evidence of antagonism among dioxin-like PCBs (Harper, N. et al., manuscript); that is, the net effect of mixtures of these congeners is less than a simple summation of TEF concentration products. Moreover, even if TEFs for some congeners are additive for some particular endpoint, there is insufficient data to support the extrapolation to equivalent TEFs and their additivity for other endpoints. We urge caution regarding the use of TEFs, and recommend more clarity regarding the mixed nature of exposures, particularly in human populations.

Limited implications of receptor theory. Receptor theory predicts that binding of dioxins to the Ah receptor may be linear at very low exposures, so some binding may occur even at near-vanishing-point doses. However, this theory does not predict the shape of the dose–response curve for any biochemical or toxic response. In particular, it does not predict that responses will result whenever binding occurs. Thus, responses may exhibit thresholds.

There is insufficient scientific evidence to support EPA's alarming conclusion.

Cancer. Although dioxin has been shown to cause cancer in laboratory animals, the epidemiologic link between exposure and increased human cancer risk is inconclusive at present. Where positive associations have been observed (*1*, *2*), they are weak, even among persons with presumed heavy exposure arising from chemical manufacturing processes or industrial accidents. Attributing cancer excesses observed among workers to their presumed dioxin exposures is questionable given the workers' known exposures to carcinogens such as asbestos and 4-aminobiphenyl. Furthermore, control for the influences of cigarette smoking and other cancer risk fac-

0013-936X/95/0929-31A$ . . © 1994 American Chemical S . . VOL. 29, NO. 1, 1995 / ENVIRONMENTAL SCIENCE & TECHNOLOGY

tors has been inadequate. Although EPA emphasizes the positive associations that have been reported, conflicting evidence cannot be dismissed and alternative explanations cannot be ruled out.

Developmental, reproductive, and endocrine effects. When considered carefully, the reports of adverse developmental effects in rodents and humans show fundamental inconsistencies. Because high-dose *in utero* exposures result in the feminization of imprinted male rat mating behavior (3), EPA argues that similar effects can be expected in humans. However, sexual behavior patterning in rodents is fundamentally different from that in humans; this endpoint is therefore of questionable relevance for potential human risks. Other developmental effects have been noted in humans and other primates, but only at doses so high as to cause maternal toxicity.

There is no evidence that dioxin exposure compromises immune function in humans.

Inclusion of endometriosis as a potential adverse effect is premature. The association of endometriosis with dioxin exposure has been reported in one study of monkeys (4), but only *a posteriori*, and alternative causes (i.e., previous exposures to other substances and surgical treatments) cannot be ruled out. Furthermore, a contradictory report (Arnold, D. L. et al., manuscript) showing no association between exposure to dioxin-like PCBs and the incidence of endometriosis in monkeys is not considered in the current draft. Such selective emphasis does not accurately reflect the full weight of the scientific evidence.

Evidence not conclusive

Endocrine disruption has been cited as another adverse outcome of dioxin exposure, but the evidence is for high doses and even then is very weak. For example, one study reported a significant increase in the prevalence of low total serum testosterone in the third exposure quartile, but this finding was not confirmed in the highest quartile, and the test for trend was not significant (5). Another report citing decreased glucose tolerance (6) has been neither peer-reviewed nor confirmed.

These limited observations may be suggestive, but they are not sufficient to conclude that people are at risk of reproductive, endocrine, or developmental effects at or near current body burdens.

Immunological effects. There is no evidence that dioxin exposure compromises immune function in humans. In animals, effects have been noted only at high doses or with protocols that do not evaluate normal immune function (e.g., injection challenges with sheep red blood or tumor cells). Effects on immunological surrogate markers (e.g., distribution of T-cell subsets and surface marker expression) have been reported in some animal experiments, but these markers have no known significance for the immune competence of the animals. In exposed humans, such effects have not been found.

Biochemical changes. If, as EPA suggests, the "average" human body burden is currently within an order of magnitude of the level required to elicit adverse effects, then sensitive biochemical markers should already be elevated in the general population. A sensitive marker that has been detected in most tissues, including human placenta, is the induction of cytochrome P4501A1. Induction of this enzyme was markedly evident in placentas from the highly exposed (Yusho and Yu-Cheng cohorts) or smoking mothers (7–9), but it has not been detected in the general nonsmoking population. It seems implausible that adverse health effects would occur at background body burdens if these subtle biochemical changes have not been observed.

Conclusion. In summary, we do not believe that there is sufficient scientific evidence to conclude that adverse human health effects should be expected at or near current background body burdens. We urge the scientific community to examine the issues carefully. A credible and scientifically defensible estimate of potential human health risks from exposure to dioxin-like compounds will emerge only after a thorough and critical peer review.

References

(1) Fingerhut, M. A. et al. *N. Engl. J. Med.* **1991**, *324*, 212–18.
(2) Bertazzi, P. A. et al. *Epidemiol.* **1993**, *4*(5), 398–406.
(3) Mably, T. A. et al. *Toxicol. Appl. Pharmacol.* **1992**, *114*, 97–107.
(4) Rier, S. E. et al. *Fund. Appl. Toxicol.* **1993**, *21*, 433–41.
(5) Egeland, G. M. et al. *Am. J. Epidemiol.* **1994**, *139*, 272–81.
(6) Sweeny, M. H. et al. "Prevalence of Diabetes and Elevated Serum Glucose Levels in Workers Exposed to 2,3,7,8-Tetrachlorodibenzo-*P*-Dioxin (TCDD)", 12th International Symposium on Dioxins and Related Compounds, Tampere, Finland, August 1992.
(7) Lucier, G. W. *Environ. Toxicol. Chem.* **1991**, *10*, 727–35.
(8) Wong, L. K., Sloop, T., Lucier, G. W. *Toxicol. Appl. Pharm.* **1986**, *85*, 60–68.
(9) Fumio, T. et al. *Cancer Res.* **1984**, *44*, 3916–23.

The ENVIRON Expert Panel on Dioxin Risk Characterization is a group of scientists assembled by the ENVIRON Corporation on behalf of the American Forest and Paper Association (AF&PA) to conduct a rigorous peer review of EPA's risk characterization of dioxin. Previous expert panels have commented on the draft state-of-the-science chapters issued by EPA and the epidemiologic literature on dioxin. Support for these panels has been provided by AF&PA without regard to the outcome of the panel deliberations. Panel members are Raymond S. Greenberg, Emory University, School of Public Health; Joseph Margolick, Johns Hopkins University, School of Hygiene and Public Health; Donald R. Mattison, University of Pittsburgh, School of Public Health; Peter Munson, Silver Spring, MD; Allan B. Okey, University of Toronto, Department of Pharmacology; David J. Olive, Yale University School of Medicine, Department of Obstetrics and Gynecology; Alan Poland, University of Wisconsin–Madison, Department of Oncology; and Joseph V. Rodricks, Larisa Rudenko, and Thomas Starr, ENVIRON Corporation, Arlington, Va.

Incinerators Targeted by EPA

New limits proposed for biggest dioxin generators

JEFF JOHNSON

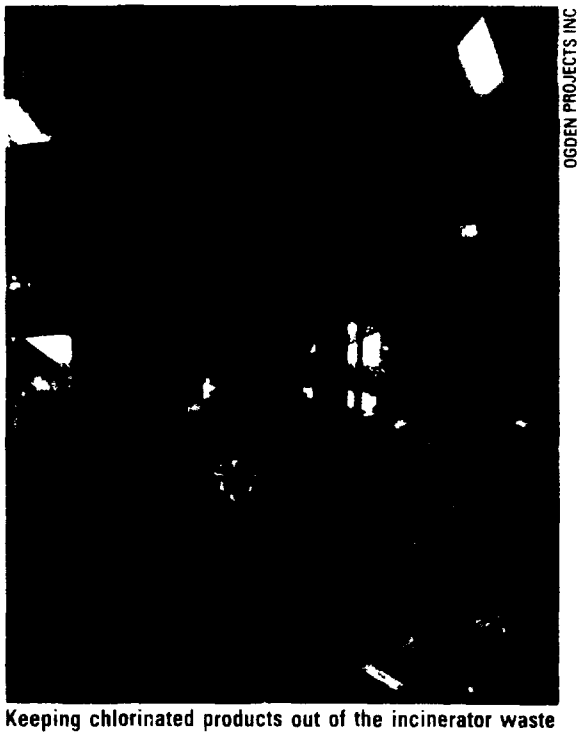
When EPA officials announced the results of the dioxin draft reassessment last September, they homed in on one particular industry for regulatory action—waste incinerators—and laid out plans to cut dioxin emissions drastically over several years. The proposed limits, together with the heightened concern about health effects from dioxin revealed by the reassessment, have breathed new life into an old debate over incinerator emissions and how to control them.

Environmental groups have long called for cutting what goes into an incinerator, be it paper, lead batteries, or chlorine-based products that produce dioxin when burned. The Agency, however, decided to come out with limits based on what can be achieved by emissions controls, rather than rely on waste stream limits or similar "pollution prevention" approaches. That choice is sure to be discussed as EPA considers a final technological solution to cut dioxin emissions.

"Waste combustion accounts for about 95% of all the known dioxin emissions," Lynn Goldman, EPA assistant administrator for prevention, pesticides, and toxics, said in September when releasing the draft reassessment. "Medical and municipal waste combustion dominates combustion sources," she added. However, she said that any overhaul of environmental regulations based on the draft reassessment must wait until the draft is finalized in September 1995. Meanwhile, EPA will continue to "move forward in implementing its dioxin control programs," and at the top of EPA's list, according to Goldman, are incinerators.

Demonstrating Agency action, Goldman pointed to proposed air pollution control regulations for some 171 municipal solid waste (MSW) incinerators issued under a court order Sept. 1, 1994 (*Federal Register*, 1994, 59, 48198, *Federal Register*, 1994, 59, 48228), and an upcoming proposal for 6700 burners of medical waste, which EPA is under court order to issue by February.

The MSW and hospital waste proposals are expected to be similar and based on the same technology. Goldman said that once implemented, the regulations would cut emissions by 99% for the worst polluters. The MSW proposal would cover many smaller units for the first time and would bring all incinerators up to new standards. For medical waste incinerators, the proposal will set the first federally required controls.



OGDEN PROJECTS INC

Keeping chlorinated products out of the incinerator waste stream is the strategy environmental groups are advocating to reduce dioxin emissions

These two incinerator types contribute 20–50% of all dioxins that drift to Earth through air deposition, according to EPA's exposure estimate. Some 8100 g of dioxin per year come from these incinerators out of a total of 9400 g emitted to the atmosphere by all incinerator

What Happened to Pulp and Paper?

Notably missing from this latest dioxin debate is the pulp and paper industry. Once the proverbial bad guy in the dioxin controversy because of its toxic emissions to lakes, streams, and oceans from the pulp-bleaching process, the nation's paper industry appears to be slipping off EPA's radar screen as it implements measures to cut chlorine use and reduce dioxins.

Cleanup in this industry, characterized by EPA as the nation's third largest polluter, is being driven by a proposed air–water "cluster" regulation that would cut annual dioxin emissions from 300 g to 30 g. The proposed rule does not call for compliance until 1998, but the industry is shifting from elemental chlorine pulp-bleaching processes to more benign ones and plans to cut dioxin emissions to water to "nondetect" levels by 1996, says Barry Polsky, of the American Forest and Paper Association. But Polsky says the industry *must continue to use some chlorine for pulp bleaching.*

However, 50 environmental groups want the industry to move to totally chlorine free (TCF) pulp bleaching, eliminating all dioxin emissions, according to Jessica Landman, an attorney with the Natural Resources Defense Council. "Smart companies," Landman says, "should get out of the chlorine-using regulatory universe."

Despite the U.S. industry's professed reluctance to endorse TCF pulp, sections of the paper and pulp industry are quietly considering the advantages, several industry sources say. But so far, most large companies see TCF pulp and paper only as a "niche" market that does not merit the costs of new equipment and processes.

Several industry officials say this may change, and if it does, the industry will follow the lead of Louisiana Pacific's Somoa, CA, pulp mill as well as that of four or five smaller U.S. TCF mills.

Archie Beaton, director of the Chlorine Free Products Association, a trade group of paper companies, printers, and others in the paper industry, says there are 68 TCF mills in the world, but fewer than a dozen are in North America. He predicts that number will grow as pulp mills find it difficult to comply with cluster regulation emissions limits without dumping chlorine and as paper makers discover that customers want to buy paper made with TCF pulp. The industry, Beaton says, has even come up with a new logo for chlorine-free products: three dolphins chasing each others' tails.

—JEFF JOHNSON

sources, EPA says. These figures are mid-point averages with huge variances, however. The Agency believes 2900–22,700 grams per year may come from all known anthropogenic air sources. But when unknown sources and recirculating dioxin are counted, EPA says as much as 50,000 g may be raining down each year on the United States. These figures are in "toxic equivalents" (TEQ) for all dioxins and furans, based on the toxicity of 2,3,7,8-TCDD.

No cause for panic

Noting the variance in estimates and unmeasured and unknown sources, scientists point to the uncertainty of the figures, and critics—particularly those in the regulated community—charge that incinerator operators are unfairly singled out. However, EPA officials note that air deposition of dioxin affects the most people and is the pathway with the greatest impact on human health through bioaccumulation in the food chain. Although there was "no cause for fear and panic," Goldman noted, "there was cause for government to move forward on controlling risks."

The proposed MSW incinerator regulations would reduce emissions to a level now achieved by the top 12% of U.S. incinerators, EPA says, using a combination of air scrubbers and baghouses coupled with injection of activated carbon to capture dioxins and "good operating procedures" to limit their formation. The proposal is scheduled to become final in September 1995, and operators will have up to three years to comply. The dioxin requirements are part of a general regulatory package to limit all emissions from these burners. EPA says compliance with the rule will cost the industry $450 million and force 60% of incinerator operators to install new scrubbers.

The proposed medical waste incinerator standards are expected to shut down many small, on-site operations, a boon for commercial incinerator companies that hope to step into the void.

The regulations, EPA says, will cut annual MSW dioxin emissions to 30 g from 3000 g, and similar reductions are expected from medical waste burners that produce some 5100 g per year. But the technology-based emissions controls upon which the emissions limits are based are primarily "end-of-pipe" techniques, something EPA has pledged to avoid. And although less dioxin will go out the smokestack, it is unclear how much less will actually be generated or how much will be captured and shifted from air to ash to landfill.

The Agency's decision to rely on controls rankles environmentalists. "EPA is relying on the discredited strategy of sticking a control on a source of pollution," says Barry Commoner, director of the Center for Biology of Natural Systems, Queens College, City University of New York. "Instead of attempting to recapture the dioxin in a stack-gas scrubber—which is never perfect and only shifts the problem from stack emissions to fly ash precipitated in the scrubber—dioxin production can be prevented by using intensive recycling programs."

Chlorine critics

Commoner targets chlorinated products, especially those made from polyvinyl chloride (PVC) that are high in chlorine. He urges that these products be kept out of the waste stream or that fewer be produced. "In the long run, as long as chlorine is used, there will be dioxin," he says.

Environmentalists also say the proposed standards are too weak and not reflective of reductions achievable by top-performing MSW incinerators. They advocate immediate implementation of toughened emissions limits. But the overall focus of Greenpeace, the Natural Resources Defense Council, the Sierra Club, and others is on a general reduction in chlorine use in plastic and paper products and, at a minimum, a mandatory national recycling program for plastics to keep most chlorinated products out of incinerator feedstock.

"It is not just recycling but redesigning the makeup of toxic sources," Marjorie Clarke, a solid waste consultant with INFORM (New York City), says. "We should be substituting less toxic sources—in particular, phasing out polyvinyl chloride and paper bleached with chlorine. Add scrubbers and do the rest, but we've got to do more than that."

Environmentalists have been joined by a heterogeneous chorus of dioxin and chlorine critics from the Great Lakes International Joint Commission to

health groups such as the American Public Health Association, the Michigan State Medical Society, and the Genesee County (Flint, MI) Medical Society.

But William Carroll, a staff scientist with the Chlorine Chemistry Council of the Chemical Manufacturers Association, disagrees: "Removing plastics from the waste stream may be a good thing to do but it won't make much difference in dioxin emissions."

Further complicating an assessment of the role of chlorinated products in dioxin generation and the benefits of removing them from the waste stream are conflicting studies cited by both sides (*1–4*).

Emission controls

Meanwhile, EPA is moving ahead on incinerator emissions controls and has developed dioxin limits based on what its engineers think a state-of-the-art MSW incinerator can achieve. In explaining current MSW incineration theory, David Cleverly, an EPA environmental scientist, and John Schaum, chief of EPA's exposure assessment methods branch, emphasize that dioxin formation depends in large part on what happens in the seconds after trash is burned in the primary combustion chamber. Although some dioxin is found in municipal waste and not destroyed during the burn, this is probably not a major source, they say. More frequently, dioxins are formed during thermal breakdown and molecular rearrangement of chlorinated compounds, organic materials, and trace metals during and after incineration.

Dioxin formation requires chlorine to be available in some form in the MSW feedstock, but the actual formation of dioxin takes place away from the combustion chamber after gases, fly ash, and miscellaneous combustion products have began to cool and condense. For instance, when a material high in chlorine, like PVC, is burned, hydrogen chloride gas, chlorinated benzene, or other compounds that may help form dioxin are created. Dioxin itself is formed as the flue gas moves away from the combustion zone and into flue gas cleaning equipment.

Dioxin forms best at about 300 °C after combustion gases leave the 1000 °C combustion zone. Currently, the best pollution control technologies rely on systems to block dioxin formation by rapidly cooling postincineration gases with a spray dryer and collecting dioxin that does form with a scrubber after it is bound to fly ash or activated carbon. Cleverly notes that "in an ideal system, you would prevent dioxin from being formed. That would be pollution prevention." Good combustion practices and use of a spray dryer to cool gases would fall into the category of pollution prevention, according to Cleverly. Among other systems in the pollution prevention realm, Cleverly says, are technologies to collect hydrogen chloride gas before it leaves the combustion zone and systems for adding sulfur-based compounds that could stop the dioxin formation process.

These technologies and others that cut the amount of dioxin generated are being evaluated by EPA and industry scientists, says James Kilgroe, manager of EPA's municipal waste combustion program.

EPA is building a pilot-scale incinerator at Research Triangle Park to learn more about the formation of dioxin and to test dioxin inhibitors and the effect of temperature. A major objective of the research incinerator, Kilgroe says, will be to determine the effect of waste composition on the formation of dioxin.

When asked whether data support removing PVCs and plastics, Kilgroe says, "There is no conclusive evidence that removing certain components will have a major effect on emissions. There is still enough chlorine available in the waste to form dioxins, and removing plastics will probably not reduce emissions to levels required by EPA's proposal."

Recycling option

Schaum and Cleverly emphasize, however, that the regulations do not prevent a community from trying to reduce dioxin emissions by limiting plastics, PVCs, or other chlorine sources in the waste stream. But it is up to the community or incinerator company to put such a program together, although the proposed regulation does require communities to investigate recycling plans that could include the removal of chlorinated wastes when new incinerators are sited.

One problem with removing chlorinated wastes, according to industry and EPA sources, is that plastics burn well. Along with paper, they contribute most of the heat content in municipal solid waste refuse, and their removal would result in a very low Btu and inefficient operations, especially for waste-to-energy incinerations.

"What would you have left to burn?" an EPA source asks. "When you reduce the heat content of fuel, it will be more difficult for incinerators to run economically and to generate sufficient energy through the wastes."

Less waste to burn and the loss of an efficient fuel, along with new emissions standards, is a scenario the incinerator industry does not want to see, especially as the costs of its chief competitor, landfills, keep looking cheaper to city officials.

A recent case the industry hopes to avoid repeating is that of an 11-year-old incinerator in Columbus, OH. Last year, EPA found that the Columbus incinerator was one of the nation's largest dioxin emitters, pumping some 900 g of dioxin TEQ into the air each year, about 30 times more than the Agency hopes all 171 MSW incinerators will emit once the new regulations are in place. The cost to comply with the proposed regulations was said to be $65 million. Meanwhile Ohio landfills were charging $32 a ton to take in trash; the incinerator needed $49 a ton to break even—without the new equipment.

"When we first built the plant we assumed that landfill acreage would shrink, the price of electricity would increase, and recycling would not cut our source of waste," says Kirk McCoy, public affairs official at the plant. "None of that happened. Now we can't pay off the incinerator." In November the facility's directors voted to shut the plant down.

References

(1) Boerekamps-Kanters, J.; Louw, R. Final Report RUL-VROM Project, Department of Chemistry, University of Leiden, The Netherlands, 1993

(2) Johnke, B.; Stelzner E. *Waste Manage Res* **1992**, *10*, 345

(3) Mark, F. *Association of Plastics Manufacturers in Europe Technical Paper* 1994

(4) Theisen, J. et al. *Chemosphere* **1989**, *19*, 423

Jeff Johnson is an associate editor on the Washington staff of ES&T