Overview of exposure, toxicity, and risks to children from current levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds in the USA

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Received 19 May 2005; accepted 4 August 2005

Abstract

Studies of children indicate that exposure of the general population to low levels of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) does not result in any clinical evidence of disease, although accidental exposure to high levels either before or after birth have led to a number of developmental deficits. Breast-fed infants have higher exposures than formula-fed infants, but studies consistently find that breast-fed infants perform better on developmental neurologic tests than their formula-fed counterparts, supporting the well-recognized benefits of breast feeding. Children receive higher exposures to PCDD/Fs from food than adults on a body-weight basis but those exposures are below the World Health Organization's tolerable daily intake. Laboratory rodents appear to be at least an order of magnitude more sensitive than humans to the aryl hydrocarbon receptor-mediated effects of these substances, which makes them poor surrogates for predicting quantitative risks but makes them good models for establishing safe levels of human exposure by organizations mandated to protect public health. Any exposure limit for PCDD/Fs based on developmental toxicity in sensitive laboratory animals can be expected to be especially protective of human health, including the health of infants and children. Because body burdens and environmental levels continue to decline, it is unlikely that children alive today in the USA will experience exposures to PCDD/Fs that are injurious to their health.

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Keywords: Dioxins; Furans; TCDD; Children; Health risk; Risk management

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Abbreviations: Ah, aryl hydrocarbon hydroxylase; ATSDR, US Agency for Toxic Substances and Disease Registry; C.I., confidence interval; EPA, US Environmental Protection Agency; FAO, Food and Agriculture Organization; FDA, US Food and Drug Administration; FT4, free thyroxine; HxCDF, hexachlorodibenzo-furan; IQ, intelligence quotient; MOE, margin of exposure; MRL, minimal risk level; PCBs, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-p-dioxins; PCDF, polychlorinated dibenzofurans; PCDD/F, polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans; PeCDF, pentachlorodibenzofuran; RfD, reference dose; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TDI, tolerable daily intake; TEF, toxic equivalency factor; TEQ, toxic equivalence quotient*; TT3, total triiodothyronine; TT4, total thyroxine; WHO, World Health Organization.

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1. Introduction

Since risk management aimed at reducing emissions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds was initiated in the 1970s, substantial decreases in environmental levels and in body burdens have been observed. Although somewhat uncertain due to changes in analytical methodologies over time, available data on emissions, environmental and food levels, and tissue levels indicate a several-fold reduction in exposures and body burdens since 1970 (Hays and Aylward, 2003). The US Environmental Protection Agency (EPA) reported that emissions from quantified sources—such as waste incineration, pesticide manufacture, and chlorine bleaching of pulp and paper—decreased from more than 14,000 g TEQ1/year in 1987 to about 1500 g TEQ/year in 2000—a 90% decrease—and are expected to continue to decline (EPA, 2005a). Human body burdens of TCDD in the US decreased 10-fold and dioxin TEQ decreased 4–5-fold between 1972 and 1999, due to the long elimination half-lives of dioxins and dioxin-like compounds—polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/Fs)—implying a decrease in exposure of more than 95% (Hays and Aylward, 2003). EPA has estimated that more than 90% of the remaining human exposures to PCDD/Fs occur through food consumption, primarily from animal fat (EPA, 2004). PCDD/Fs are not deliberately added to food or created during food processing. Natural sources of PCDD/Fs, such as forest fires, contribute to a background level of exposure from food (EPA, 2004), as may unregulated anthropogenic sources such as uncontrolled burning of household waste in barrels (Lemieux et al., 2003). The EPA has been debating the extent to which PCDD/Fs pose risks to health since 1990; no risk estimate or exposure limit is agreed upon.

Risk management of PCDD/F emissions was initiated because of concerns about its potential carcinogenicity, but concerns have broadened to include other potential human health effects, such as developmental toxicity. Children receive higher doses of PCDD/Fs from food than adults on a body-weight basis (FDA, 2004; Charnley and Doull, 2005) but eliminate PCDD/Fs more rapidly than adults (Kreuzer et al., 1997). Both fat and serum levels of PCDD/Fs have been found to increase with age (Falk et al., 1999; Luotamo et al., 1991) although they are decreasing with time. Nonetheless, children may be subject to higher potential risks from PCDD/Fs than adults because they are still developing.

This paper examines the available evidence relevant to evaluating health risks to children during childhood from PCDD/F exposure and toxicity and draws conclusions about the extent to which current risk management practices account for age-related differences in risk.

2. Sources of children’s PCDD/F exposure

2.1. Food

Like adults, children’s primary source of exposure to PCDD/Fs is food, mostly from meat and dairy products. Based on the US Food and Drug Administration’s (FDA’s) Total Diet Study and on the US Department of Agriculture’s most recent food consumption survey (1994–1996 and 1998 Continuing Survey of Food Intakes by Individuals), estimates of PCDD/F intake for the total US population and for three age groups of children have been made (Charnley and Doull, 2005). Those intake estimates are shown in Table 1. On a body-weight basis, young children have two to three times higher intakes, older children have about twice the intake, and teenagers have the same or lower intakes.
Table 1
Mean and upper-percentile PCDD/F intake estimates for the total US population and for children 2, 6, and 14–16 years of age assuming non-detects are equal to LOD/2 or to zero

<table>
<thead>
<tr>
<th>Intake (pg TEQ/kg BW/day)</th>
<th>Non-detects = LOD/2</th>
<th>Non-detects = 0</th>
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<tbody>
<tr>
<td><strong>Total US population (N = 20,607)</strong></td>
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<tr>
<td>Mean</td>
<td>0.38</td>
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<td>90</td>
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<td>95</td>
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<td>99</td>
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<td><strong>Children 2 years (N = 1056)</strong></td>
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<td>Mean</td>
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<td>90</td>
<td>1.92</td>
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<td>99</td>
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<td><strong>Children 6 years (N = 570)</strong></td>
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<tr>
<td>Mean</td>
<td>0.93</td>
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<td><strong>Males 14–16 years (N = 300)</strong></td>
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<tr>
<td>Mean</td>
<td>0.50</td>
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<td><strong>Females 14–16 years (N = 293)</strong></td>
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<tr>
<td>Mean</td>
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<td>99</td>
<td>0.90</td>
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Mean PCDD/F intake estimates are based on consumption data from the 2004 Total Diet Study Per Capita. Consumption and intake per body weight is based on an average body weight per age group. Upper percentiles of PCDD/F intake estimates are based on weighted 2-day average per capita consumption data from the 1994–1998 CSFII. Each individual's intake per kilogram body weight is calculated using each individual's body weight as opposed to an average body weight per age group. Values in italics do not meet minimum sample size criteria for this type of analysis as established by the National Centers for Health Statistics. Source: Charnley and Doull (2005).

Another source of uncertainty is the absence of data on coplanar (dioxin-like) polychlorinated biphenyls (PCBs), which contribute to the TEQ used as the basis of the TDI but have not yet been analyzed as part of FDA’s food contaminant survey. Forthcoming FDA data are hoped to resolve this omission. However, like PCDD/Fs, total PCB levels in food and in human adipose tissue and serum have been declining (ATSDR, 2000). If coplanar, congener-specific PCB data were available for the US, they would most likely be below the analytic limit of detection in most foods and tissues sampled (similar to PCDD/Fs) and their activity would likely be modulated by the less planar (non-dioxin-like) PCBs (Safe, 2001). Nonetheless, the addition of coplanar PCBs to the dietary intake estimates might result in more estimates exceeding the TDI. However, the relevant value for comparison to a TDI is the lifetime daily intake, not the daily intake at one particular age. Given the much lower daily intakes during adolescence and adulthood and the fact that environmental levels continue to decline, the likelihood that children alive today in the US will experience lifetime daily intakes exceeding the TDI is negligible.
2.2. Human milk

PCDD/F concentrations in human milk have been declining. Data from Germany, Norway, and the Netherlands indicate that concentrations have decreased by at least 50% since 1980 (LaKind et al., 2001). Overall, however, few human milk samples have been analyzed for PCDDs and PCDFs. Because most analyses that do exist were performed a decade or more ago, mostly in Europe (Kreuzer et al., 1997), the results are not representative of current US exposures, which are much lower based on recent human lipid serum levels (Patterson et al., 2004). More recent data from Taiwan (2000–2001) found mean concentrations of PCDD/Fs and PCBs in milk of 10.5 and 14.5 ng TEQ/kg lipid for women less than 29 years of age and 29 years or older, respectively (Chao et al., 2004). Two pooled US milk samples had 12 ng TEQ/kg lipid for combined PCBs and PCDD/Fs (Wang and Needham, 2003). No similar recent data could be located on PCDD/F levels in US human milk from which breast-fed infants’ current exposures could be directly estimated. The data of Wang and Needham (2003) are consistent with the most recent serum lipid data from people under 40 (5–10 ng TEQ/kg lipid) (Patterson et al., 2004). Because PCDD/Fs are more or less in a balance between the fat in serum and the fat in human milk (Wittsiepe et al., 2004), that concentration range can be used as a surrogate to estimate intake from human milk. Assuming that US breast-fed infants consume approximately 800 g milk daily in the first four to five months of life, that human milk contains approximately 20–50 g lipid/l, and that the density of milk is 1.03 (NAS/IOM, 1991), PCDD/F intakes estimated from more recent data range from about 80 to 400 pg TEQ/day.

PCDD levels in human milk vary within and between nursing periods and decline over time after birth, with 1,2,3,4,6,7,8,9-octachlorodibenzo-\(p\)-dioxin declining more rapidly than other PCDDs (Fürst et al., 1989). Because the variation and decline are seldom reflected in milk sampling data, which tends to involve a single time point shortly after birth, actual exposures are likely to be lower (Slorach and Jensen, 1991; LaKind and Berlin, 2002). Other sources of uncertainty associated with estimates of PCDD/F levels in human milk arise from pooling milk samples and from inconsistent sampling and analytical methods. The extent to which infants are breast-fed also varies, with differences associated with socioeconomic status and ethnicity (Wright et al., 1988; Forste et al., 2001). The majority of infants are weaned by 6 months of age (Wright et al., 1988).

2.3. Pharmacokinetics/dose issues

The half-life of TCDD and presumably other PCDD/Fs is age-dependent and greatly influenced by the lipid content of the body. Because of their rapid growth, infants and young children dilute their body burdens of persistent chlorinated organic compounds, including PCDD/Fs. The half-life of TCDD is about 4 months in infants, increasing to 5 years at age 40; in older adults, a range of 6.9–9.7 years has been reported in different studies involving varying levels of exposure (Michalek et al., 1996). Recent blood and human milk data on five PCDD/F congeners in addition to TCDD were used to calculate elimination half-lives of less than 6 months in infants for all six congeners (Leung et al., in press). The authors concluded that the much shorter half-lives in infants compared to adults are attributable to rapid growth of the adipose tissue volume and enhanced fecal excretion of dioxins for breast-fed infants. The results also explain why infants’ higher daily PCDD/F intake during breast feeding does not translate to proportionately higher infant tissue concentrations.

Metabolic elimination of TCDD is not important in infants. Most TCDD is excreted unchanged in feces. The concentration of TCDD in fecal lipids reflects the concentration of TCDD in lipids elsewhere in the body (Rappe and Anderson, 1992). The extent to which other PCDD/Fs are metabolized in infants is unknown. TCDD and other chlorinated compounds can cross the placenta and have been detected in the tissues of stillborns and in neonatal cord blood. The concentrations of PCDD/Fs in fetal lipids are the same as their concentrations in maternal lipids (Kreuzer et al., 1997). TCDD and other chlorinated compounds pass through the placenta and can be detected in the tissue of stillborns and in cord blood of neonates. Kreuzer et al. (1997) found TCDD levels in stillborns ranging from 1.3 to 2.1 ng/kg lipid in adipose tissue and from 0.76 to 1.5 ng/kg in liver lipids. TCDD levels in breast-fed infants ranged from 0.38 to 4.1 ng/kg lipid in adipose tissue. Levels were lower in formula-fed infants, ranging from 0.16 to 0.76 ng/kg. The length of breast feeding varied in these infants. Other PCDDs and PCDFs were also measured. Among individual children the levels of total PCDDs in adipose tissue lipids varied greatly, ranging from 16.19 to 112 ng/kg in formula-fed infants and from 25.36 to 423 ng/kg in breast-fed infants.

Based on data in the literature from stillborn infants and infants dying of sudden infant death syndrome in Germany, considering the decline of PCDDs and PCDFs in breast milk over time, and making assumptions about the levels of TCDD in milk at birth, Kreuzer et al. (1997) developed and tested a model. The measured and predicted values in human milk agreed fairly well. Based on this model, TCDD body burden decreases over the first year after birth in formula-fed infants but then increases, reaching a peak at 16 years of age. In contrast, TCDD body burden increases after birth in breast-fed infants, decreasing rapidly for 3 years
after weaning and reaching the same level as formula-fed infants at 7 years of age. Kreuzer et al. (1997) concluded that although TCDD body burdens increase during breast feeding, they do not remain elevated and do not exceed levels observed in adults. The authors estimated that subsequent TCDD levels remained around 2–3 ng/kg serum lipid through the end of life.

Abraham et al. (1998) found similar results in four German breast-feeding infant–mother pairs, noting a distinct accumulation of PCBs and PCDD/Fs in infants throughout 6–7 months of breast feeding, with infants’ serum levels 2–4 times those of the mothers at one year of age. Although the pharmacokinetics of most of the other congeners have not been extensively studied, they would also be preferentially stored in lipids and most likely excreted by first order kinetics. The most recent data in the US (1996–2001) indicate that current body burdens of total chlorinated coplanar congeners (PCDD/Fs and PCBs) range between 6 and 12 ng TEQ/kg serum lipid in people under 40 (Patterson et al., 2004).

A similar model to that of Kreuzer et al. (1997), using the same data but slightly different assumptions, was developed by Lorber and Phillips (2002) and included both breast-fed and formula-fed infants. The authors also assumed that the lipid content of infants’ bodies increased from 14% body weight at birth to 23% at 1 year of age, with the half-life of TCDD increasing from 4 months to over 1 year during that period. Their results indicated that body burdens of nursing infants do not exceed those of adults.

The results of both the Kreuzer et al. (1997) and Lorber and Phillips (2002) models are likely to overestimate of true children’s body burdens because breast feeding tends to decline rapidly after 6 months (Wright et al., 1988). In addition, the human milk TCDD data used in these models were obtained over a decade ago, mostly in Europe, or involved groups with unusual exposures, so are much higher than would be expected in the US today.

3. Health effects of PCDD/Fs of relevance to children

Based primarily on information obtained from laboratory animals, concerns have been raised that exposures to PCDD/Fs could be associated with a variety of effects potentially relevant to children, including cancer, developmental toxicity, immunotoxicity, and reproductive toxicity. Although most of the information available on potential age-related differences in the toxicity of PCDD/Fs comes from experiments in laboratory animals, a number of epidemiologic studies have evaluated the effects of children’s exposure to PCDD/Fs. In general, studies of children indicate that exposure of the general population to low levels of these chemicals does not result in any clinical evidence of disease. However, studies of children exposed accidentally to high levels of PCDD/Fs either before or after birth have reported a number of developmental deficits.

3.1. Human studies: poisoning incidents

Following the 1976 reactor vessel explosion at a chemical plant in Seveso, Italy that contaminated the surrounding countryside with high levels of TCDD, 1500 children who had been 6–10 years old at the time of the accident were studied clinically over a period of 6 years (Mocarelli et al., 1986). A total of 4500 laboratory tests were performed in these children, primarily liver function tests, serum lipid analysis, and urinary δ-aminolevulinic acid determinations. All results were within the normal reference range, although some of the most highly exposed children excreted more L-gluturonic acid for the first 4 years after exposure, suggesting that their hepatic microsomal enzymes may have been induced. Based on the clinical tests performed, the authors concluded that the acute phase of TCDD intoxication in Seveso passed with no appreciable consequences for children. However, an age-related difference in susceptibility to chloracne may have been observed. No chloracne was seen in adults with levels of TCDD below 10,400 ng/kg serum lipid, while some children with one-tenth that level of TCDD did develop chloracne. Several outcomes among subjects living close to the plant and subjects with chloracne have been followed (Mocarelli et al., 1991; Bertazzi et al., 1998; Bertazzi et al., 2004):

- Between 1976 and 1979 immunologic effects in 48 children from the most highly contaminated zone and 48 control children were compared. The exposed children had higher rates of lymphocytic responses to phytohemagglutinin and pokeweed mitogen and increased numbers of peripheral lymphocytes (Bertazzi et al., 1998). While suggestive of an immunologic effect, these findings could not be appropriately interpreted because of design limitations and poor compliance among controls.
- Infants born between 1977 and 1982 were examined for the presence of malformations. An increased risk for birth defects was not observed. Similarly an examination of fetal losses found no association with exposure (Bertazzi et al., 1998).
- Mocarelli et al. (1996) reported a change in sex ratio following exposure, with an excess of female offspring between 1977 and 1984 among children born to parents with high TCDD serum concentrations in 1976. There were 26 males and 48 females born during that time; however, TCDD serum concentrations were measured in only nine sets of parents. A difference in sex ratio no longer existed between 1985 and
1994, during which 60 males and 64 females were born. This transient difference reported in the number of males and females could have been due to sampling error because the number of children born was relatively small, although an exposure-related effect cannot be ruled out.

- Mocarelli et al. (2000) investigated the sex ratio of the offspring of 239 men and 296 women in whom TCDD serum levels were determined. A total of 346 girls (51.3%) and 328 boys (48.6%) were born to potentially exposed parents between 1977 and 1996. The probability of female births increased with increasing paternal TCDD serum levels. The number of fathers in each group was small, however, potentially resulting in sampling errors.

- A retrospective women’s health study evaluated endometriosis among women who were 30 years old or younger at the time of the accident and had resided in close proximity to the plant when the accident occurred (zones A and B) (Eskenazi et al., 2002). Among the 601 participants, the median serum TCDD levels were 257 ppt (ng/kg lipid) (range, 114–713 ppt) in zone A and 47 ppt (ng/kg lipid) (range, 22.5–220 ppt) in zone B. Nineteen of the women were identified as having endometriosis, 277 did not have endometriosis, and the remaining women were of uncertain status. The relative risk ratio for women with serum TCDD levels of 20–100 ppt (ng/kg lipid) was 1.2 (90% CI, 0.3–4.5) and for women with TCDD levels above 100 ppt (ng/kg lipid) was 2.1 (90% CI, 0.5–8.0). These findings were not statistically significant and the confidence intervals were wide. Pregnancy outcomes were examined in 510 of these women (Eskenazi et al., 2003). Of the 888 pregnancies reported, 97 (10.9%) ended in spontaneous abortions. There was no association between log_{10} serum TCDD level and term birth weight or births that were small for gestational age.

- Warner et al. (2004) found that individual serum TCDD levels among the 282 women who were premenarchal at the time of the accident were not significantly related to the time when menarche occurred. That conclusion held true when the 84 women who were younger than 5 years of age at the time of the accident were evaluated separately (Warner and Eskenazi, 2005).

- Because abnormal tooth development had been reported following PCDF poisoning incidents elsewhere (see below), Alaluusua et al. (2004) recently compared the teeth of 48 highly exposed individuals 25 years after the explosion in Seveso to 65 matched individuals from the control area. Only one of the study subjects (10%) with TCDD serum lipid levels of 31–226 ng/kg at the time of the accident had developmental defects in enamel. At serum levels of 238–592 ng/kg this anomaly was observed in 5 (45%) of the study subjects and at serum levels of 700–26,000 ng/kg 9 (60%) of the study subjects had this defect. Among the controls 26% showed the defect. The prevalence of anomalies was higher among individuals who were less than 5 years old at the time of the accident. An increased prevalence of hypodontia was also observed in this study population. According to the authors over 100 factors have been listed as being responsible for developmental defects of enamel. The authors concluded that, despite the apparent dose–response relationship observed, many of the dental defects seen in their study population may have been unrelated to TCDD exposure. Furthermore, because of the small number of study subjects, the power of the study to detect aberrations was poor given that these effects occur spontaneously and with relatively high frequency.

In another acute poisoning episode, 1850 people in Japan (Yusho disease) and more than 2000 people in Taiwan (Yucheng disease) were affected as a result of ingesting rice oil contaminated with a number of chlorinated organic compounds including PCDDs and PCDFs (Kuratsune, 1989). Exposure data are poor, but concentrations of PCDFs were in the ppm (mg/kg) range in the rice oil and in the ppb (µg/kg lipid) range in human blood and tissues. In affected children, the eruption of permanent teeth was delayed and teeth with abnormally curved roots were observed. There have been anecdotal reports of hyperpigmentation, deformed pigmented nails, Meibomian gland hypersecretion, chronic bronchitis, and lower birth weights occurring among children born to mothers within several years after the incidents in both Japan and Taiwan (Kuratsune, 1989; Rogan et al., 1988). Rogan et al. (1988) examined 117 children born to affected mothers in Taiwan and 107 unexposed controls. The children were a few months to 6 years old when examined. As a group the exposed children were shorter, weighed less, and had a history of natal teeth (9% vs. 0% in controls), gum hypertrophy (6% vs. 0%), chipped teeth (11% vs. 2%), and pigmented deformed nails (16% vs. 1%).

Yucheng children also showed delays in achievement of developmental milestones. For example, exposed children had lower scores in many developmental tests compared to unexposed children; however, the differences were not always statistically significant and did not correlate with PCDF body burdens or clinical signs of poisoning (Lai et al., 1994). Studies of intelligence quotient (IQ) found a consistent 5-point decrement when individual exposed children were compared to controls (Chen et al., 1992). The mean IQ scores of both groups fell below 100 (88–96), however, suggesting that retarded children (IQ 50–70) were included in both groups or that the children were too young to be tested. The authors found no detectable PCDFs in 21 of the exposed and
15 of the control children who had taken these tests. Thus, it is not possible to causally associate the results of these tests with PCDF exposure. More recently, a 3-point difference in IQ between Yucheng children and controls was reported (Lai et al., 2002). All of the available studies of developmental neurotoxicity suffer from uncertain or non-existent exposure estimates and from confounding.

Yu et al. (1998) examined immune function in 105 Yucheng children and 101 controls, finding no differences 16 years after in utero exposure in the parameters examined (serum immunoglobulin levels, cell-mediated immunologic analysis), although the exposed children had been reported to have had more frequent respiratory and ear infections early in life. Chao and Hsu (1997) found that 42.7% of the Yucheng children they examined and 18.8% of controls had abnormal tympanic membranes (p < 0.003). Measurable levels of PCDFs in the children with middle ear problems ranged from 50 to 1400 ppt (ng/kg lipid) and of hexachlorodibenzofuran (HxCDF) from 100 to 3200 ppt (ng/kg lipid). Children with middle ear disease had significantly higher levels of PCDFs (p = 0.022). The range of PCB levels was the same for children with and without ear disease. These and other studies are summarized in Kimbrough and Krouskas (2001).

In a recent review of Yusho and Yucheng, Guo et al. (2004) provided additional exposure information that was obtained from children between 1979 and 1981. Those children had average levels of 6940 ng 2,3,4,7,8-pentachlorodibenzofuran (PeCDF)/kg lipid and 20,800 ng 1,2,3,4,7,8-HxCDF/kg lipid. In 1992, approximately 14 years after exposure, the average serum level in 56 Yucheng mothers was 1090 PeCDF ng/kg lipid and 2560 ng HxCDF/kg lipid. Young men who had been exposed in utero to such high levels had normal semen volume and sperm counts but there was abnormal morphology (37.6% vs. 25.9%) and reduced motility (35.1% vs. 57.1%). It is unclear whether the differences resulted from exposure or from the way the specimens were collected and handled.

Ryan et al. (1990) estimated that the mean uptake or body burden of 2,3,4,7,8-PeCDF equivalents associated with nausea and anorexia in Yusho patients was 4.4 μg/kg body weight and the amount associated with chloracne was 5.9 μg/kg body weight. A similar body burden of 4.0 μg/kg body weight was estimated for Yucheng patients, which is equivalent to 2 μg TCDD/kg body weight or about 10 μg TCDD/kg body fat. According to Ryan et al. (1990), there is some uncertainty about the quantitation of 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF in the contaminated oil and in adipose tissue because the saponification process used in the analyses by some laboratories under hot alkali conditions resulted in a decrease in the total PCDF and partially dechlorinated congeners. In addition, because the chemical analyses for PCDD/Fs and coplanar PCBs are tedious and expensive, few specimens were analyzed. The analytical methodology for these particular chemicals was not available in 1968 when the Yusho episode occurred and in its infancy when the Yucheng outbreak took place. Many of the specimens were collected many years after the outbreaks occurred. For these reasons the data are uneven and often not correlated with clinical signs and symptoms.

The predominant PCDF isomers present in the Yucheng and Yusho poisoning incidents were the more toxic isomers, namely 2,3,7,8-, 1,2,4,7,8-, 2,3,4,7,8-, and 1,2,3,4,7,8-PCDF. 2,3,7,8-TCDF is also highly toxic, however, 2,3,4,7,8-pentachlorodibenzofuran has the longest half-life in humans, is predominantly bound to proteins in the liver, and may have a greater chronic toxicity than 2,3,7,8-TCDF. In Seveso the people exposed accidentally were exposed only to 2,3,7,8-TCDD, the most toxic PCDD congener. In the general population children’s PCDF body burden is 5–7 times lower than that of PCDDs (Kreuzer et al., 1997), and most of the PCDD/Fs present are the less toxic isomers.

3.2. Human studies: environmental exposures

Potential effects of PCDD/Fs on neurologic development have been studied in several cohorts of children exposed to background environmental levels via their mothers’ milk. Those studies were summarized by Kimbrough et al. (2001). For example, in one study in the Netherlands, a group of 418 mother–infant pairs were recruited and evaluated for neurodevelopmental indices postnatally (Huisman et al., 1995). Maternal blood was collected in the last month of pregnancy and cord blood immediately after delivery. Human milk was collected as a 24-h sample in the second and sixth week and, if possible, 3 months after delivery. Plasma samples were analyzed for four non-planar PCB congeners and milk samples were analyzed for 17 2,3,7,8-substituted PCDDs and PCDFs, three planar PCB and 23 non-planar PCB congeners. A total of 20 of the 394 examined children were considered neurologically suspect and four children were considered abnormal. Higher levels of planar PCBs in breast milk were associated with a higher incidence of hypotonia. Higher levels of PCBs, PCDDs, and PCDFs in milk were associated with reduced neonatal optimality. The birth weights of all infants were within the normal range. Using the Bayley scales, lower psychomotor indices (PDI) in infants with higher PCB/PCDD levels were noted at 3 but not at 7 or 18 months of age (Koopman-Esbeboom et al., 1996). However, breast feeding compensated for any early negative effects on the PDI. At 42 months of age the cognitive abilities of these infants were within the mean standard variation score or higher, with breast-fed children scoring higher than formula-fed children.
In this and other studies, when investigators controlled for breast-feeding, socioeconomic status, and parental education, neurodevelopmental deficits were limited to formula-fed children, suggesting that PCB and PCDD/F exposures did not play a role. These results are consistent with the widely recognized benefits of breast feeding.

Reports of neurodevelopmental delay and impairment related to high levels of perinatal PCDD/F exposure has generated the hypothesis that PCDD/Fs may exert adverse neurodevelopmental effects via disruption or alteration of thyroid hormone activity during pregnancy (Winneke et al., 2002; Zoeller, 2003). For example, Kooiman-Esseboom et al. (1994) reported small changes in thyroid hormone measures in pregnant mothers and their infants exposed to background levels of PCDDs and PCBs in the Netherlands. A reference range from the laboratory where the tests were performed was not provided. According to the authors the thyroid function parameters tested in all mother–infant pairs were within the normal range for age-appropriate controls. However, within this normal range PCDD and PCB TEQ levels in milk were significantly correlated with lower maternal TT3 and TT4 levels and with higher infant plasma TSH levels in the second week and third month after birth (p < 0.05). At the age of 3 months no significant differences in the infants' plasma TT3, TT4, or FT4 levels were found. Birth weights were within the normal range. This and other studies are discussed in detail in Kimbrough and Krouskas (2001). Although some studies have reported statistically significant thyroid function alterations correlated with exposure to PCDDs, they have all been only slight variations within the normal range. Thyroid hormone levels during the neonatal period change over time, as do lipid levels and PCDD levels in human milk. The variations reported are within the range of normal variation of the data and should not be construed as predictive of human health effects (Kimbrough and Krouskas, 2001).

Studies of the potential impacts of PCBs, PCDDs, and PCDFs on immune function have been performed in Europe among children with background body burdens in the ppt (ng/kg lipid) range (Kimbrough and Krouskas, 2001). The children studied showed either no increase in the prevalence of infections or were afforded some protection against infections associated with breast feeding. All tests of immune function parameters were within the normal range, although some test results for children with slightly higher chemical measurements were at the upper end of normal. For example, ten Tusscher et al. (2003) reported the results of a study in 27 8-year-old Dutch children with perinatal PCDD/F exposure. Increases in CD4 T helper cells and CD45 RA cells were seen in relation to perinatal exposure. Persistently decreased platelet counts and increased thrombopoietin were seen in conjunction with postnatal exposure. However, all of the reported variations were within the normal laboratory range of the general pediatric population.

No human data are available to assess whether exposure to PCDD/Fs early in life have an impact on cancer incidence later in life. However, because PCDD/Fs are considered to be tumor promoters in laboratory animals, not tumor initiators, children would be less susceptible than adults because they would have fewer potential initiated targets.

3.3. Laboratory animals

There is a large body of literature on the reproductive and developmental effects of PCDD/Fs and related compounds in laboratory animals, although most studies have focused on 2,3,7,8-TCDD. Reviews of that literature and of PCDD/Fs' other effects in animals are available (ATSDR, 1998; AEA Technology, 1999; EPA, 2004). Developmental effects on the reproductive system are the effects that occur at the lowest doses in many laboratory animals, so those effects have been considered by several organizations to be the most sensitive end point of concern for evaluating human risk. The extent to which the laboratory animal data are relevant to humans is controversial, however, in part because human developmental stages do not map well to rodent development (WHO, 1986; NAS, 2003) (see below). Nonetheless, EPA (2004) has concluded that the dose–response relationships reported in some PCDD/F studies in laboratory animals yield burden ED01s for neurobehavioral and other developmental effects that are below current average human body burdens. The accuracy of ED01 estimates is also controversial due to their dependence on study design and to the difficulty inherent in identifying such a small change (1%) above background rates, especially for continuous endpoints.

Most of the developmental effects observed in laboratory animals associated with PCDD/F exposures involve the reproductive system of both male and female animals, primarily rats. Low prenatal doses of TCDD have been associated with decreased sperm production in male rats when they reach adulthood, with demasculinized and feminized sexual behavior, and with reduced ventral prostate weight (Mably et al., 1992a,b,c; Faqi et al., 1998; Ohsako et al., 2001; Simanainen et al., 2004). Reduced ovarian weights and morphological reproductive alterations involving structural malformations in the urogenital tract and external genitalia occur in female rats prenatally exposed to TCDD (Gray and Ostby, 1995; Gray et al., 1997). Developmental effects on the reproductive system have also been reported in hamsters and mice. Cross-fostering studies indicate that the majority of developmental effects on the reproductive system in rats are induced as a consequence of expo-
sure before birth, rather than lactation exposure after birth (Lilienthal and Winneke, 1991). The antiestrogenic effects of PCDD/Fs may account for at least some of their reproductive effects, although the mechanisms of toxicity are not yet fully understood. The human relevance of the developmental effects reported in laboratory rodents is questionable because rodent pups were exposed as a result of a single maternal gavage dose on day 15 of pregnancy, while human fetal exposure is steady state.

Developmental immunologic effects resulting from perinatal exposure to TCDD (thymic atrophy, cell-mediated immune suppression) have also been reported in rats (Gehrs and Smialowicz, 1997).

Prenatal exposure of Rhesus monkeys to low doses of TCDD has been reported to induce developmental neurobehavioral effects (Schantz and Bowman, 1989; Schantz et al., 1992) and endometriosis (Rier et al., 1993), although the latter study did not report daily intake adequately and was confounded by high levels of coplanar PCBs (JECFA, 2001). The effect of TCDD on endometriosis has been hypothesized to involve modulation of immune and endocrine function (Rier and Foster, 2002). The neurobehavioral effects included cognitive deficits and changes in social interaction, and were considered the most relevant sensitive effect for evaluating human health risk by the US Agency for Toxic Substances and Disease Registry (ATSDR) (ATSDR, 1998).

3.4. Mode of action

Effects of PCDD/Fs are generally attributed to their initial interaction with the aryl hydrocarbon hydroxylase (Ah) receptor. While interaction with the Ah receptor appears to be necessary for most of the PCDD/Fs' biological effects, alone it is insufficient to account for all of those effects. Binding to the Ah receptor mediates up-regulation of xenobiotic enzymes such as the P450 cytochromes, which are responsible for both activating and detoxifying potentially toxic substances. The P450 cytochromes are expressed in more than 17 isoforms, with expression varying according to developmental stage. For example, while CYP2E1 is expressed in hepatic tissue in the second trimester and reaches adult expression levels in infants at three months of age, CYP1A2 is not expressed until several months after birth (McCarver, 2004). Due to the delay in expression of most P450 enzymes, young infants might be less susceptible to the effects of PCDD/Fs that are mediated by P450 enzymes than older children or adults. However, the relationship between Ah receptor interaction and subsequent mechanisms of action for critical effects such as developmental and reproductive toxicity are not yet fully understood.

Ah receptor ligand binding affinity varies in different strains of mice. Comparison of the human and murine Ah receptor amino acid sequences shows that the polymorphism responsible for reduced ligand binding affinity in resistant mouse strains is characteristic of the human Ah receptor as well, suggesting that the binding affinity of the human Ah receptor may be more like that of non-responsive than responsive mouse strains (Schmidt and Bradfield, 1996; Roberts et al., 1986; Lorenzen and Okey, 1990). Human cells have consistently required approximately 10-fold higher concentrations of TCDD in vitro than rodent cells to respond with enzyme induction (Conner and Aylward, in press). Recent studies of in vivo enzyme induction-related endpoints in human populations with moderately and highly increased TCDD body burdens detected no relationship between these endpoints and TCDD body burdens at body-burden levels up to 250 ng TEQ/kg body weight, or approximately 25 times above the upper range of current general population background body burdens, while marked elevations in enzyme activity were observed in persons with body burdens above 750 ng TEQ/kg. In contrast, the more sensitive laboratory rodent strains and species exposed to TCDD exhibit significant enzyme induction at body burdens below 50 ng/kg. TCDD induces some cytochromes in monkeys at doses as low as 3 ng/kg body weight. These interspecies data on the most sensitive and well-understood response to binding of TCDD and related compounds to the Ah receptor are consistent with the binding affinity and molecular structure data and support the hypothesis that the human Ah receptor is less functional than that of the more sensitive laboratory animals at a molecular level (Conner and Aylward, in press). Abraham et al. (2002) estimate that humans are likely to be one to two orders of magnitude less sensitive to the Ah-receptor-related effects of TCDD than rats and monkeys.

4. Limiting PCDD/F risks

Risk management of PCDD/F emissions was initiated because of concerns about its potential carcinogenicity, but concerns about other potential human health effects, such as developmental toxicity, have since been raised. EPA has been considering the nature and extent of health risks from PCDD/Fs since 1990; no risk estimate or exposure limit is agreed upon. No acceptable daily intake has been established by FDA. Meanwhile, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has proposed a tolerable monthly intake of 70 pg TEQ/kg BW as being protective of human health by virtue of providing an adequate margin of safety for the developmental reproductive effects observed in male rats exposed prenatally to 2,3,7,8-TDCDD (see Section 3) (JECFA, 2001). That monthly intake translates to a tolerable daily intake (TDI) of
2 pg TEQ/kg BW. The UK Food Standards Agency’s Committee on Toxicity has recommended a TDI of 2 pg TEQ/kg BW (UK FSA/COT, 2001), as has the European Commission’s Scientific Committee on Food (EC, 2001) (although their specific recommendation is 14 pg TEQ/kg BW/week), consistent with the JECFA TDI. The US ATSDR has developed a minimal risk level (MRL) for chronic exposure to 2,3,7,8-TCDD of $1 \times 10^{-9}$ mg/kg/day (1 pg/kg/day), based on reports of developmental neurotoxicity in monkeys (ATSDR, 1998).

TDI is defined by the World Health Organization as “an estimate of the amount of a substance in food or drinking-water, expressed on a body weight basis…that can be ingested on a daily basis over a lifetime without appreciable health risk” (WHO, 2003). In general, a TDI is established using a no-observed-adverse-effect level or benchmark dose identified from the laboratory animal toxicity test that produced the most sensitive effect, which is adjusted downwards by dividing by uncertainty factors intended to produce a TDI protective of the most sensitive people. That is, exposure at or below the TDI is expected to produce no health risk, even in people who may be more susceptible to toxicity than others. However, because of the way the TDI is derived, exposure above this level does not imply that a health risk is expected. JECFA TDIs are essentially identical in both definition and method of estimation to EPA’s reference doses (RfDs). ATSDR MRLs, defined as estimates of “daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse non-cancer health effects,” are derived similarly.

Because developmental reproductive toxicity in rats and developmental neurotoxicity in monkeys exposed to TCDD prenatally are considered the most sensitive effects that have been reported, the various international TDIs and the ATSDR MRL were derived based on those effects. The TDIs and the MRL may thus be considered protective of children and the developing fetus because, while it can be the case that the fetus and the newborn are more sensitive to toxicity than older children or adults, so are developing laboratory animals. Exposure limits based on developmental endpoints in laboratory animals are anticipated to protect developing humans as well (Scheuplein et al., 2002).

In its recent draft risk assessment (EPA, 2004), EPA chose not to establish an explicit exposure limit, relying instead on a margin-of-exposure (MOE) approach to evaluate potential risks from PCDD/Fs. A margin of exposure is a ratio determined by dividing a dose or exposure level affecting a given percentage of humans or test animals (such as a benchmark dose) by the corresponding actual or estimated human dose or exposure level. Larger margins of exposure are more desirable than smaller margins of exposure because they indicate a larger difference between the dose known to produce toxicity and the actual dose. The adequacy of a particular margin of exposure is determined by evaluating a number of factors, such as the slope of the dose–response relationship in the observable range, mode of action, nature and extent of uncertainties, human variation in susceptibility to the response of concern, and human sensitivity as compared with laboratory animals (EPA, 2004; Risk Commission, 1997). When margins of exposure are small, reaching any conclusion regarding the certainty of harm versus no harm is difficult and must rely heavily on scientific judgment regarding the adequacy of the available data (EPA, 2004).

Based on laboratory animal data, EPA has concluded that the MOEs for PCDD/Fs at current background levels are 10 or less for both cancer and non-cancer effects. For the most sensitive effects observed in laboratory animals, EPA MOEs range from less than one for enzyme induction in mice and rats, to less than 4 for developmental effects, to 4 for endometriosis in non-human primates. Evaluating the significance of such MOEs in terms of human health requires taking into account:

- the likelihood that the effects observed in laboratory animals are relevant to humans;
- the likelihood that humans are more or less sensitive to PCDD/F-related toxicity than laboratory animals;
- the fact that the MOEs were estimated on the basis of average intakes or body burdens for the population as a whole and not for children, who have lower body burdens but higher intakes than adults;
- data indicating that current intakes and body burdens are lower than those assumed by EPA.

It is likely that given our current knowledge of exposures, body burdens, sensitivity, and human relevance, today’s children are at considerably lower risk from PCDD/Fs than they might have been two or three decades ago and at appreciably lower risk than suggested by the MOEs calculated by EPA in its 2004 draft risk assessment (EPA, 2004).

EPA has recently finalized supplemental cancer risk assessment guidance addressing the need to account for the potentially disproportionate contribution of exposure to mutagenic carcinogens early in life to lifetime cancer risk (EPA, 2005b). This guidance requires weighting early life exposures to mutagenic carcinogens to increase their estimated contribution to lifetime cancer risk. The guidance applies only to mutagenic carcinogens, however, and PCDD/Fs are not considered mutagenic (EPA, 2004). Thus, although EPA concludes in its most recent draft risk assessment for PCDD/Fs that such mixtures are likely human carcinogens (EPA,
adjustment to compensate for early life exposure is not warranted.

The fact that EPA has not identified a quantitative exposure limit for PCDD/Fs does not mean that EPA has failed to manage adequately the potential risks from those substances. Efforts to limit emissions of PCDD/Fs begun in the 1970s have resulted in strict controls on most of the known and quantifiable major industrial sources of PCDD/F releases. As a result of efforts undertaken by EPA, state governments, communities, and private industry, known and quantifiable industrial emissions in the US have been reduced by more than 90% from 1987 levels (EPA, 2004; EPA, 2005a). EPA has used its authority under the Safe Drinking Water Act and Clean Air Act to limit PCDD/F exposures by promulgating, for example, the 1997 “Cluster Rule” addressing the pulp and paper industries and establishing technology-based emissions standards for various waste incinerators [63 FR 18504-18751, April 15, 1998 and 63 FR 42238-42240, August 7, 1998]. EPA estimates that municipal waste incinerators emitted collectively nearly 18 pounds of dioxin TEQs in 1987 but are now expected to emit less than 1/2 ounce per year. Similarly, medical waste incinerators emitted a total of about 5 pounds of dioxin TEQs in 1987 but are now limited collectively to about 1/4 ounce annual emissions. The pulp and paper industry continues to reduce emissions to air and has virtually eliminated PCDD/Fs in its wastewater discharges. Reduced industrial emissions are reflected by decreasing body burdens, with TCDD decreasing 10-fold and dioxin TEQ decreasing 4–5-fold between 1972 and 1999 (Hays and Aylward, 2003). EPA has also used its authority under the Toxic Substances Control Act to require chemical manufacturers to submit data on manufacturing processes that might produce PCDD/Fs and under the Federal Insecticide, Fungicide and Rodenticide Act to address PCDD/F contamination of pesticides.

These and other successful risk management actions have reduced environmental and human tissue levels of PCDD/Fs substantially over the last several decades. US exposures now approach natural background levels, although a few unregulated anthropogenic sources remain.

5. Discussion

Infants’ principal exposure to PCDD/Fs occurs through human milk, with formula-fed infants exposed to lower levels than breast-fed infants. Breast-fed infants’ exposures decline rapidly after weaning, however, and studies of the potential neurodevelopmental effects of exposure have found that formula-fed infants score lower on intelligence and vocabulary tests than their breast-fed counterparts (Mortensen et al., 2002). Formula-fed infants are at increased risk of developing childhood cancer, asthma, ear and respiratory infections, allergies, diabetes, and gastrointestinal infections compared to breast-fed infants (Fomon, 2004; Young, 2004). Human milk is the optimal sole infant food for the first 6 months of age (AAP, 1997).

Children’s principal exposure to PCDD/Fs occurs primarily through food, as does that of adults. Children’s exposures are higher on a body-weight basis than adults’, but elimination in children occurs more rapidly than in adults, and children’s exposures do not exceed limits that are considered protective of public health established by a number of international organizations. Those limits are protective of children’s health as well as adults’ because they were established on the basis of developmental toxicity, the most sensitive effect presumed relevant to human health observed in exposed laboratory animals.

The extent to which PCDD/F-induced developmental toxicity observed in laboratory animals is relevant to human toxicity is questionable for several reasons. EPA (2004) has concluded on the basis of the observations described here that because differentiated tissues derived from ectoderm—namely skin, conjunctiva, nails, and teeth—are sites of action of halogenated aromatic hydrocarbons in transplacentally exposed human infants, the CNS, also a highly differentiated tissue derived from ectoderm, should be considered a potential site of TCDD action. In support of this possibility, EPA cites evidence that the central nervous systems of mice transplacentally exposed to 3,3′,4,4′-tetrachlorobiphenyl, monkeys perilatally exposed to TCDD, and children transplacentally exposed to a mixture of heat-degraded PCBs in the Yucheng incident are affected. All of those effects were observed at exposure levels that were much higher than those that occur as a result of current environmental exposures. There is little or no evidence of PCDD/F-related effects at environmental levels of exposure. Although some statistically significant differences have been reported for several effects when analysis of variance or regression analysis was performed, the differences were limited to variations within the normal range of the observations or measurements. While statistically significant, the variations are unlikely to be relevant biologically. Furthermore, reported findings were inconsistent among studies, which suggests that factors other than PCDD/F exposures may have been responsible for the results (Kimbrough and Krouskas, 2002). Thus while it is clear that exposure to levels of PCDD/Fs several orders of magnitude higher than current background levels, resulting from acute poisoning, may adversely affect infants and children in several ways, the available clinical evidence does not provide adequate support for a relationship between adverse effects and exposure to background levels of PCDD/Fs.
One reason for the lack of clinical evidence of adverse effects at environmental levels of exposure may be that humans are less sensitive to the toxic effects of PCDD/Fs than most laboratory animals (Kimbrough, 1990). There are several lines of evidence supporting lower human sensitivity. One is that compared to humans, subhuman primates have very little adipose tissue, which makes them more sensitive to PCDD/Fs because, being unable to store these chemicals in adipose tissue, they concentrate them in target tissues instead. Other evidence includes the facts that human Ah receptor binding affinity resembles that of non-responsive mouse strains and, unlike rats and monkeys, human cytochrome induction requires high exposures.

Another issue complicating conclusions about human risk is that human and rodent developmental stages are difficult to compare. Human infants are much more mature than rats, mice, and hamsters when they are born, and some stages of development that take place in laboratory animals after birth have already occurred in the human fetus before birth. Human infants have more adipose tissue than infant rodents. Rat milk contains higher levels of PCDD/Fs than human milk at equivalent exposures because of the higher fat content of rat milk. Rats also consume more milk on a body-weight basis than humans and grow more rapidly (WHO, 1986).

Thus, responses in laboratory animal species generally are not quantitatively the same as those expected in humans and may also be different depending on the timing of exposure and the target organ. These differences must be taken into account when predicting human risk from PCDD/Fs. The fact that laboratory animals are more sensitive than humans and poor surrogates for predicting quantitative risks makes them good models for establishing safe levels of human exposure. Any exposure limit based on a sensitive end point in laboratory animals can be expected to be especially protective of human health, including the health of potentially sensitive individuals or life stages. The 2 pg TEQ/kg BW/day TDI for PCDD/Fs established by international organizations is thus likely to be more than adequate to protect both public health in general and children’s health in particular. In turn, because US children’s intakes of PCDD/Fs fall below the TDI and current body burdens are so low, health risks to US children from PCDD/Fs are unlikely.

Acknowledgments

This paper was written with the partial support of a grant from the Food Industry Dioxin Working Group, a Washington, DC-based ad hoc coalition of associations representing farmers, ranchers, feed manufacturers, meat processors, and food processors that had no control over the content.

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