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Development of an oral cancer slope factor for Aroclor 1268

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Abstract

Rodent cancer bioassays indicate that substantial differences exist among PCB mixtures in terms of tumorigenic response, although no bioassay has been conducted with Aroclor 1268. The USEPA has used data from these studies to develop three sets of PCB cancer slope factors (CSFs) ranging from 0.07 to 2.0 $(mg/kg\text{-}day)^{-1}$. Selection of the appropriate CSF for risk assessment purposes is largely a function of the exposure circumstances rather than the PCB mixture involved. Since the congener composition of Aroclor 1268 differs substantially from that of the predominant PCB mixture (Aroclor 1254) used to derive the CSFs, the validity of applying existing CSFs to Aroclor 1268 is questionable. We have therefore undertaken the task of developing cancer potency estimates specifically for Aroclor 1268. Potency estimation approaches for Aroclor 1268 were based in part on existing potency estimates for other PCB mixtures, coupled with the relative 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalents (TEQ) content and bioaccumulation potential of PCB mixtures. As such, both Ah-dependent and independent mechanisms of tumorigenesis were considered relevant. Both empirical evidence and mechanistic considerations indicate Aroclor 1268 is substantially less toxic and carcinogenic than the PCB mixtures that have been used by the USEPA to develop CSFs. The present analysis indicates that Aroclor 1268 is likely to be 1–2 orders of magnitude less potent than Aroclor 1254 in terms of potential tumorigenicity. Therefore, we suggest an upper-bound cancer potency factor of 0.27 $(mg/kg\text{-}day)^{-1}$ for Aroclor 1268, a value that is 7- to 8-fold lower than the USEPA's current default, but nonetheless adequately conservative.

Keywords: Aroclor 1268; Polychlorinated biphenyls; Toxic equivalency factors; Toxic equivalents; Cancer slope factor; Risk assessment

1. Introduction

PCB mixtures have been tested for potential carcinogenicity in cancer bioassays in rats and mice, and a number of studies have tried to gain insight into PCB carcinogenicity in humans by examining causes of mortality among PCB exposed workers. Collectively, the data from humans are equivocal—some studies have found excesses of specific cancer types, but no cancer type is consistently elevated across studies. In some cases, increases in cancer incidence among PCB-exposed workers were not clearly related to the extent of PCB exposure and/or did not demonstrate appropriate latency, making their association with PCBs tenuous. Reviews of these studies by both the USEPA and IARC have concluded that PCB mixtures are probably carcinogenic to humans, based on "sufficient" evidence of carcinogenicity in animals and "limited" or "inadequate, but suggestive" evidence in humans (IARC, 1987; USEPA, 1996).

The quantitative assessment of cancer risk from PCBs is based entirely upon data derived from laboratory animals, principally bioassays of PCBs in rats. Several commercial PCB mixtures have been tested for carcinogenicity from lifetime exposure, most recently examined in two reports (Brunner et al., 1996; Mayes et al., 1998) on the tumorigenicity of Aroclors 1016, 1242, 1254, and 1260 in rats. These authors demonstrated that Aroclor 1254 showed the peak potency for liver tumors while the other higher chlorinated (Aroclor 1260) and lower chlorinated mixtures (Aroclors 1242 and 1016)

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had lower potencies. Aroclor 1268 was not among the PCB mixtures tested, and no chronic bioassay data currently exist with which to directly obtain a cancer slope factor (CSF) for this commercial mixture. This is unfortunate given that rodent cancer bioassays indicate that there are substantial differences among PCB mixtures in terms of tumorigenic response that might be predicted based on differences in congener make-up. For example, Aroclor 1268 (like Aroclor 1260) is expected to have a lower content of the more potent tetra-, penta-, and hexachlorinated biphenyls (Anderson, 1991; Hutzinger et al., 1974), and accordingly a much lower TCDD toxic equivalents score compared to Aroclor 1254.

The current USEPA cancer slope factors (CSFs) for estimating potential cancer risk from PCBs are based largely on findings for the most potent mixture, Aroclor 1254 (IRIS, 2004). Since the congener composition of Aroclor 1268 is dramatically different from Aroclor 1254, we believe that extending the generic CSFs to this mixture would not be scientifically appropriate. Therefore, the objective of this study was to examine the relationship between PCB congener composition and tumorigenicity such that a CSF estimate for Aroclor 1268 could be derived.

2. Summary of the basis for USEPA'S PCB cancer potency estimates

Several studies examined tumor responses in mice and rats subjected to less-than-lifetime exposure to PCB mixtures ranging from 42 to 60% chlorine content (Ito et al., 1973; Ito et al., 1974; Kimbrough et al., 1972; Kimbrough and Linder, 1974; Kimura and Baba, 1973; Rao and Banerji, 1988). In general, these studies were negative or found an increase in pre-neoplastic lesions, but no increase in carcinomas. While less-than-lifetime studies can offer useful information, lifetime exposure is usually regarded as necessary for adequate assessment of potential carcinogenicity and for development of quantitative cancer potency estimates. PCB mixtures of 42, 54, and 60% chlorine content have been tested in conventional rodent cancer bioassays with lifetime exposure, and the results of these bioassays are summarized in Table 1. All of the bioassays were conducted in rats, usually with both sexes. Collectively, the results show positive responses in females and negative responses in males with 42% chlorine PCB mixtures and positive responses in both males and females with 60% chlorine PCB mixtures. Two studies of Aroclor 1254 gave conflicting results, one was essentially negative in both males and females (NCI, 1978) and the other was negative in males but strongly positive in females (Brunner et al., 1996). The reason for this discrepancy is not clear, but may relate to differences in composition of the Aroclor 1254 material used in these studies or the rat strain in which these different batches of Aroclor mixtures were tested.

Potential differences in cancer potency among different commercial mixtures are illustrated by the study of Brunner et al. (1996). This is the only study to examine more than one commercial mixture, and in fact four mixtures were included in the analysis—Aroclors 1260, 1254, 1242, and 1016. Each commercial mixture was tested in both male and female rats. In its cancer dose–response assessment for PCBs, the USEPA fit data from this and other studies to derive the estimated dose associated with a 10% increased tumor incidence (ED10) for each commercial PCB mixture, as well as the 95% lower bound estimate of the ED10, termed the LED10 (USEPA, 1996). From these values, a linear extrapolation to the origin of a dose–response plot was used to derive a central estimate of the slope (from the ED10) and an upper-bound estimate of the slope (from the

Table 1
Summary of cancer bioassay results for commercial PCB mixtures

Mixture	Results (male animals)	Results (female animals)	Reference
42% chlorine			
Clophen A30	Negative	ND	Schaeffer et al. (1984)
Aroclor 1242	Negative	Positive	Brunner et al. (1996)
Aroclor 1016	Negative	Positive	Brunner et al. (1996)
54% chlorine			
Aroclor 1254	Negative	Negative	NCI (1978)
Aroclor 1254	Negative	Positive	Brunner et al. (1996)
60% chlorine			
Clophen A60	Positive	ND	Schaeffer et al. (1984)
Aroclor 1260	ND	Positive	Kimbrough et al. (1975)
Aroclor 1260	Positive	Positive	Norback and Weltman (1985)
Aroclor 1260	Positive	Positive	Brunner et al. (1996)

"Positive" indicates a statistically significant increase in hepatocellular adenomas or carcinomas compared with control at one or more PCB doses; "negative" indicates no significant increase at any dose. ND, not determined since animals of this gender were not included in the study. All studies were in rats and were conducted for approximately 2 years.

LED10). For the purposes of converting the doses used in these studies to an equivalent human dose, the following expression was used:

$$\text{Human dose(mg/kg-day)} = \text{PCB dose(ppm in diet)} \times 0.05 \times (\text{animal weight}/70\,\text{kg human weight})^{1/4}.$$

Table 2 summarizes the cancer potency estimates for each commercial PCB mixture in both male and female rats in the Brunner et al. (1996) study. Comparisons of these cancer potency estimates result in two observations: (1) cancer potencies for all Aroclors are substantially higher in female rats than male rats; and (2) for males, potency was directly measurable for only Aroclor 1260 (the potency estimates for the other Aroclors listed in Table 2 are "best guesses" that were based on the sensitivity of the study), suggesting that it was the most potent mixture in males; while in the female animals the differences in Aroclor potency are measurable and more substantial, and the potency is greatest at 54% chlorine content.

The USEPA has used data from Brunner et al. (1996) and other studies to develop three sets of PCB CSFs ranging from 0.04 to 2.0 $(\text{mg/kg-day})^{-1}$. The PCB slope factor to be used in a particular situation is primarily a function of the exposure circumstances rather than the PCB mixture to which the individual is, or will be, exposed. According to USEPA guidance, most exposure situations for PCBs (e.g., exposure to PCB-contaminated soils) are viewed as falling under the category of "High Risk and Persistence," where CSFs of 1.0 and 2.0 $(\text{mg/kg-day})^{-1}$ are recommended as central and upper-bound values, respectively. These slope factors are taken from responses in female rats to Aroclors 1254 and 1260 and are considered to be the "highest observed potency" factors from animal studies (USEPA, 1996). The highest of the central tendency slope factor values (1.0 $(\text{mg/kg-day})^{-1}$) is based on the ED_{10} for the highest tumor incidence observed in the Brunner et al. (1996) study, i.e., that of female rats exposed to Aroclor 1254. The upper-bound CSF value derived from the LED_{10} (2.0 $(\text{mg/kg-day})^{-1}$) was selected to reflect the highest upper-bound slope factor derived in the Brunner et al. (1996) study (again that of female rats exposed to Aroclor 1254), as well as the highest upper-bound slope factor that could be derived for female rats from any chronic study (i.e., based on Aroclor 1260 in the Norback and Weltman study).

The other two sets of central tendency and upper-bound CSF estimates adopted by the USEPA are representative of the lowest and intermediate values calculated for PCB mixtures other than Aroclor 1254 that were tested in the Brunner et al. (1996) study. The USEPA recommends that these two remaining sets of CSFs be applied in the following manner: In situations of "Low Risk and Persistence," values of 0.3 and 0.4 $(\text{mg/kg-day})^{-1}$ are to be used as the central and upper-bound slope factor values, respectively, as taken from the response of female rats to Aroclor 1242 (see Table 2). Examples where these values are recommended include ingestion of water-soluble congeners, inhalation of evaporated congeners, and dermal exposure (without correction for dermal bioavailability). The third category is described as "Lowest Risk and Persistence," and is the only one that requires a characterization of the PCB congeners of the mixture. This category is defined as situations where >99.5% of the PCB congeners present in the PCB mixture has 4 or fewer chlorines. In this case, a value of 0.04 $(\text{mg/kg-day})^{-1}$ is to be used as the central tendency CSF value, and 0.07 $(\text{mg/kg-day})^{-1}$ as the upper-bound CSF. These two values are taken from the response of female rats to Aroclor 1016 in the Brunner et al. (1996) study (see Table 2).

3. Choosing a slope factor for Aroclor 1268

This approach of using the highest CSFs derived from animal studies to estimate PCB cancer risks is certainly conservative, but its validity in situations involving Aroclor 1268 contamination is questionable. There is reason to believe that congener composition is a critical determinant of the cancer potency of PCB mixtures, and that potency estimates from female animals exposed to PCB mixtures of 54% or even 60% chlorine content are not representative of the potencies of mixtures with substantially greater (or lesser) chlorination,

Table 2
Cancer slope factors for various PCB mixtures in male and female rats

PCB mixture	Cancer slope factor			
	Central estimate		Upper-bound estimate	
	Male	Female	Male	Female
Aroclor 1260	0.1	0.4	0.2	0.5
Aroclor 1254	0.06[a]	1.2	0.1[a]	1.5
Aroclor 1242	0.03[a]	0.3	0.08[a]	0.4
Aroclor 1016	0.02[a]	0.04	0.04[a]	0.07

Data from Brunner et al. (1996) as presented in USEPA (1996). Slope factors are in units of $(\text{mg/kg-day})^{-1}$.
[a] No significant increase in tumors; slope estimate based on the sensitivity of the study.

including Aroclor 1268. This conclusion is supported by the fact that in the recent USEPA re-evaluation, the upper-bound slope factors for PCB mixtures of approximately 42–60% chlorine content (Aroclor 1016 to Aroclor 1260) ranged between 0.07 and 2.2, i.e., the potency of the different mixtures varied 30-fold (USEPA, 1996).

Understanding the problem with using the USEPA default CSFs for Aroclor 1268 first requires recognition that male and female rats respond differently to PCBs. Data from the Brunner et al. (1996) study clearly suggest greater potency of PCBs in females as compared with males (see Table 2). This observation is acknowledged in the USEPA dose–response assessment, although its significance is downplayed somewhat:

> The different responses for male and female rats (Brunner et al., 1996) suggest the possibility of developing different potency values for males and females. In view of the 91 percent response in male Wistar rats (Schaeffer et al., 1984), as well as the sensitivity of male mice (Ito et al., 1973; Kimbrough and Linder, 1974), it is premature to conclude that females are always more sensitive. (USEPA, 1996)

It should be recognized, however, that the reference in the above passage to the response in male Wistar rats in the Schaeffer et al. study has confused potency with efficacy. The fact that a strong response occurred in males is not the point—it is the dose at which this response occurred and how it compares with the dose required to produce an equal response in females that is important in assessing relative potency. Since Schaeffer and colleagues did not include females in their study, this study offers nothing to contradict the concept that PCBs are more potent in females. Similarly, the cited studies in mice (Ito et al., 1973 and Kimbrough and Linder, 1974) used only males, and no inferences on relative potency between the sexes are possible. There are two studies other than Brunner et al. (1996) that examined both male and female rats—the NCI bioassay of Aroclor 1254 (NCI, 1978) and the study of Aroclor 1260 by Norback and Weltman (1985). The NCI study found little difference between the sexes, but noticeable differences are not expected in a study where the results were negative. In the study of Norback and Weltman (1985), however, where positive responses were seen in both male and female animals, the potency in females was approximately 10-fold higher than males (see Table 3-1 in USEPA, 1996). Thus, the data from which potency comparisons can be reasonably made are consistent in showing that greater potency is generally observed in female rats.

Recent analyses of data developed in the Brunner et al. (1996) study suggest that there are two mechanisms of PCB hepatocarcinogenesis, one that results from Ah-receptor mediated effects and predominates in female animals, and a second mechanism that is predominant in male animals (Brown et al., 1997, 2001). The principal evidence for this lies in the fact that the tumorigenic potency of PCBs in female rats is strongly predicted by the total 2,3,7,8-TCDD toxic equivalents (TEQ) of the PCB mixture, while potency in males appears to be unrelated to the mixture TEQ.

Aroclor 1268 contains only small percentages of the toxic tetra-, penta-, and hexachlorobiphenyl congeners (Table 3), and its TEQ value is much lower than that of Aroclors 1242, 1254, and 1260 (Tables 4 and 5). Consequently, it is reasonable to expect that Aroclor 1268's cancer potency will be much less than the potencies of these other mixtures in the more sensitive female animals. Even though an empirical cancer potency estimate for Aroclor 1268 does not yet exist, a cancer potency estimate for this mixture in female rats can nonetheless be projected based on the apparent relationship between TEQ and cancer potency demonstrated by the Brunner et al. (1996) study. That is, using the TEQ–cancer potency relationship evident in the Brunner et al. (1996) study, a cancer potency estimate can be derived corresponding to the TEQ value for Aroclor 1268. Two approaches are possible, each with slightly different mechanistic assumptions.

Table 3
Weight percentage of PCB congeners in Aroclor mixtures

Biphenyl	Aroclor 1221*	Aroclor 1232*	Aroclor 1016	Aroclor 1242	Aroclor 1248	Aroclor 1254	Aroclor 1260	Aroclor 1268
Monochloro	47.88	22.27	1.31	0.95	0	0	0	0
Dichloro	35.94	21.19	19.40	15.15	2.03	0.49	0.10	0
Trichloro	6.52	23.47	45.36	36.53	24.9	1.31	0.27	0
Tetrachloro	**1.69**	**23.37**	**32.82**	**36.07**	**51.36**	**26.81**	**4.39**	**0.51**
Pentachloro	**0.65**	**4.78**	**1.16**	**8.73**	**18.45**	**44.32**	**10.56**	**2.75**
Hexachloro	**1.09**	**0.61**	**0**	**1.11**	**2.07**	**21.85**	**40.68**	**2.08**
Heptachloro	0.43	0.50	0	0.79	1.48	4.68	33.37	8.32
Octachloro	0.06	0.12	0	0.28	0.45	0.54	9.40	40.93
Nonachloro	0	0.02	0	0.03	0.06	0.03	1.21	37.29
Decachloro	0.01	0.01	0.01	0	0	0.02	0.02	8.12

Source. Anderson (1991).

* Aroclors 1221 and 1232 contain 5.92 and 4.77% unsubstituted biphenyls, respectively.

Table 4
Toxic equivalents (μg/g) for non-ortho and mono-ortho coplanar PCBs in Aroclor mixtures based on AHH induction[a]

IUPAC No.	Aroclor 1221	Aroclor 1016	Aroclor 1232	Aroclor 1242	Aroclor 1248	Aroclor 1254	Aroclor 1260	Aroclor 1262	Aroclor 1268
81			0.001	0.0018	0.002	0.0015	0.0002	0.0001	0.0001
77	0.2	0.22	3.2	7.2	8.1	4.2	0.57	0.3	0.35
123	0.0003	0.0001	0.0024	0.006	0.016	0.052	0.011	0.0088	0.0002
118	0.0005	0.0004	0.01	0.02	0.066	0.23	0.032	0.013	0.0015
114	0.0006	–	0.015	0.03	0.11	0.39	0.003	0.0043	0.0011
105	0.075	0.068	2.7	5.9	19.8	75.9	0.49	0.84	0.26
126	–	–	3.6	11.6	40	100	9.6	12.8	2
167	0.0001	0.0003	0.0003	0.0004	0.002	0.013	0.011	0.002	0.0001
156	0.0012	..	0.007	0.01	0.026	0.38	0.14	0.034	0.0011
157		..	0.006	0.01	0.022	0.39	0.027	0.013	0.0086
169						–			–
189	–	–	0.0001		0.0002	0.0021	0.009	0.0036	0.00004
Total	0.28	0.29	9.5	24.8	68.1	182	10.9	14	2.6

[a] Reproduced from Table 3 of Hong et al. (1993).

Table 5
Toxic equivalents (μg/g) for non-ortho and mono-ortho coplanar PCBs in Aroclor mixtures based on reevaluated WHO TEFs as published by van den Berg et al. (1998)[a]

IUPAC No.	Aroclor 1221	Aroclor 1016	Aroclor 1232	Aroclor 1242	Aroclor 1248	Aroclor 1254	Aroclor 1260	Aroclor 1262	Aroclor 1268
81			..	..	..			..	0.0009
77	0.0074	0.0082	0.12	0.267	0.3	0.155	0.021	0.011	0.013
123	0.0012	0.003	0.01	0.024	0.065	0.217	0.044	0.0365	0.001
118	0.0064	0.0046	0.122	0.23	0.79	2.74	0.39	0.151	0.0182
114	0.003	0	0.08	0.175	0.58	2.075	0.015	0.0225	0.006
105	0.0068	0.0062	0.247	0.338	1.8	6.9	0.045	0.076	0.0234
126	0	0	0.9	2.9	10	25	2.4	3.2	0.5
167	0.00014	0.00043	0.00042	0.00061	0.003	0.018	0.0156	0.00284	0.00019
156	0.013	0	0.075	0.121	0.28	4.18	1.565	0.363	0.012
157	0	0	0.021	0.038	0.0825	1.44	0.1	0.047	0.032
169	0	0	0	0	0	0	0	0	0
189	0	0	0.0009	0	0.0018	0.025	0.106	0.042	0.0005
Total	0.04	0.02	1.58	4.09	13.9	42.75	4.70	3.95	0.61

[a] Source of TEFs is van den Berg et al. (1998). Toxic equivalents were calculated using the mean concentration of coplanar PCBs in Aroclor mixtures as published in Table 2 of Hong et al. (1993).

3.1. Prediction of an Aroclor 1268 slope factor assuming an Ah-receptor-dependent mechanism in female rats

The first approach assumes that tumorigenicity in the more responsive female rats is largely, if not completely, an Ah-receptor-dependent phenomenon, and that cancer potency is directly proportional to the TEQ content of the PCB mixture. The data from which an Aroclor 1268 CSF can be extrapolated are shown in Table 6. This table contains the central and upper-bound CSF values derived by the USEPA for Aroclors 1016, 1242, 1254, and 1260 using data from female rats in the Brunner et al. (1996) study. It also lists the TEQ values for these mixtures based on congener analysis of the test materials as reported by Mayes et al. (1998). To extrapolate a cancer potency estimate for Aroclor 1268 from these data, a TEQ value for Aroclor 1268 is required. Two relatively recent and complete TEQ analyses for various PCB mixtures were selected that can be used to obtain this value. Hong et al. (1993) not only published mean concentrations of coplanar PCBs in nine Aroclor mixtures, including 1268, but also computed TEQs for these nine mixtures (Table 4). The World Health Organization (WHO) International TEFs (I-TEFs) reported by van den Berg et al. (1998) are presented in Table 5. While the absolute TEQ values for specific Aroclor mixtures differed between these analyses, the relative rankings of the TEQs within each study for various Aroclors were nearly identical. As a result, the two analyses, despite their differences, provided a relatively consistent view of the comparative TEQ content of various PCB mixtures. For example, both analyses found the TEQ content of Aroclor 1268 to be only 1.43% that of Aroclor 1254. This percentage (1.43%), when applied to the TEQ content of the Aroclor 1254 mixture used in the Brunner et al. (1996) study (i.e., 47.6 μg/g, as shown in Table 6), resulted in a corresponding Aroclor 1268 TEQ of 0.68 μg/g (i.e., $0.0143 \times 47.6 = 0.68$). In other words, had Aroclor 1268 been included in the Brunner et al. (1996) study, it is

Table 6
Predicted cancer slope factors for Aroclor 1268 based on the Brunner et al. (1996) data[a]

PCB mixture	Mixture TEQ[b] (μg/g)	Cancer slope factor (mg/kg-day)$^{-1}$		Predicted cancer slope factor for Aroclor 1268[c]	
	Mayes et al. (1998)	Central estimate	Upper bound	Based on central tendency	Based on upper bound
Aroclor 1260	7.2	0.4	0.5	0.038	0.047
Aroclor 1254	47.6	1.2	1.5	0.017	0.021
Aroclor 1242	7.8	0.3	0.4	0.026	0.035
Aroclor 1016	0.11	0.04	0.07	0.247	0.433
Average ± SD including Aroclor 1016				0.082 ± 0.110	0.134 ± 0.200
(SD as percentage of mean)				(134%)	(149%)
Average ± SD excluding Aroclor 1016				0.027 ± 0.011	0.034 ± 0.013
(SD as percentage of mean)				(39%)	(38%)

[a] Cancer slope values are central tendency and upper-bound estimates from female rats only using the study by Brunner et al. (1996) as derived by USEPA (1996).

[b] The TEQ values listed in this column are those reported for the Brunner et al. (1996) study in the recent publication of this experiment by Mayes et al. (1998).

[c] The total TEQ for Aroclor 1268 was 1.43% (Hong et al., 1993; van den Berg et al., 1998) that for Aroclor 1254. Using this percentage (i.e., 1.43%) and the total TEQ of 47.6 μg/g for Aroclor 1254, the projected TEQ for Aroclor 1268 would be 0.68. Predicted CSFs for Aroclor 1268 were arrived at using the formula: [(0.68 ÷ mixture TEQ from Mayes et al. (1998)) × CSF for the mixture].

estimated that it would have had a TEQ value of about 0.68 μg/g.

This estimated TEQ of 0.68 μg/g for Aroclor 1268 is 70-fold less than that of Aroclor 1254, approximately 10-fold less than the TEQs for Aroclors 1242 and 1260, and about 6-fold larger than the 0.11 μg/g TEQ for Aroclor 1016. Using these TEQ relationships, the USEPA-derived CSFs for the Aroclor mixtures in the Brunner et al. (1996) study were adjusted assuming a linear relationship between TEQ and CSF to derive predicted CSFs for Aroclor 1268. The results, both in terms of central tendency and upper-bound estimates, are shown in Table 6. The Aroclor 1268 CSFs based on extrapolation from the three different Aroclor mixtures with the highest TEQ contents (Aroclors 1242, 1254, and 1260) were remarkably similar. When averaged across these three Aroclors, they yielded central tendency and upper-bound Aroclor 1268 CSFs of 0.027 ± 0.011 and 0.034 ± 0.013 (mg/kg-day)$^{-1}$, respectively. The degree of variance indicated by the standard deviation as a percentage of these mean values is quite low (38–39%). These Aroclor 1268 CSF estimates are 37- and 59-fold lower than the default USEPA slope factors for PCB mixtures of 1.0 and 2.0 (mg/kg-day)$^{-1}$, more accurately reflecting the fact that Aroclor 1268 is so heavily chlorinated that it is likely to have little Ah-receptor activity.

Table 6 also illustrates that inclusion of the data for Aroclor 1016 in such an analysis leads to apparently anomalous and highly variable slope factor estimates. The combination of its comparatively low TEQ content and lower CSFs than the remaining mixtures tested by Brunner et al. (1996) leads to calculated Aroclor 1268 slope factors that are 1–2 orders of magnitude higher than the respective central tendency and upper-bound estimates for the three higher TEQ mixtures. Moreover, the variance introduced by including Aroclor 1016 data leads to standard deviations that are 134–149% of the mean. These observations support the contention that the weaker cancer potency of Aroclor 1016 does not correlate well with TEQ as does the higher potency of the more chlorinated Aroclors. This suggests that the weakly positive tumor response of female rats to Aroclor 1016 may be explained by non-Ah receptor mechanisms.

As indicated above (Tables 4 and 5), different analyses yield different estimates of the TEQ values for specific PCB mixtures. For the extrapolations described above, the Aroclor TEQ values of Mayes et al. (1998) were used because they are based on the congener composition of the specific test materials used in the Brunner et al. (1996) study. However, other sets of TEQ values for these mixtures could be substituted with little effect on the extrapolated Aroclor 1268 CSF. This is illustrated in Table 7, in which TEQs for Aroclors 1260, 1254, and 1242 taken from Hong et al. (1993) and van den Berg et al. (1998) were used instead of TEQs from Mayes et al. (1998) in the extrapolation of CSFs (central tendency and upper-bound) for Aroclor 1268. The results based on Hong et al. (1993) and van den Berg et al. (1998) indicate that although the absolute TEQ values for individual Aroclor mixtures may differ markedly, the extrapolated Aroclor 1268 CSFs based on the three Aroclors with higher TEQ values (Aroclors 1242, 1254, and 1260, without 1016 data) are comparable to those developed using the TEQs of Mayes et al. (1998). This is because, as discussed above, the relationships among mixture TEQ values within a given study are relatively consistent, even though the absolute values for a given Aroclor mixture may vary between studies. Inclusion of Aroclor 1016 in the Table 7 analyses once again resulted in much higher and apparently anomalous slope factor estimates.

Table 7
Predicted cancer slope factors for Aroclor 1268 based on other TEF analyses

PCB mixture	Mixture TEQ (μg/g)		Cancer slope factor (mg/kg-day)$^{-1}$		Predicted slope factor for Aroclor 1268 TEF Source: Hong et al. (1993)		Predicted slope factor for Aroclor 1268 TEF Source: van den Berg et al. (1998)	
	Hong et al. (1993)	van den Berg et al. (1998)	Central tendency	Upper bound	Based on central tendency	Based on upper-bound	Based on central tendency	Based on upper-bound
Aroclor 1260	10.9	4.70	0.4	0.5	0.095	0.119	0.052	0.065
Aroclor 1254	182	42.75	1.2	1.5	0.017	0.021	0.017	0.021
Aroclor 1242	24.8	4.09	0.3	0.4	0.031	0.042	0.045	0.060
Aroclor 1016	0.29	0.02	0.04	0.07	0.359	0.628	1.22	2.14
CSF for Aroclor 1268 including data for Aroclor 1016		Average ± SD (SD as percentage of mean)			0.123 ± 0.159 (129%)	0.203 ± 0.287 (141%)	0.334 ± 0.591 (177%)	0.572 ± 1.046 (183%)
CSF for Aroclor 1268 excluding data for Aroclor 1016		Average ± SD (SD as percentage of mean)			0.048 ± 0.042 (88%)	0.061 ± 0.052 (85%)	0.038 ± 0.019 (50%)	0.049 ± 0.024 (49%)

Cancer slope factors are central tendency and upper-bound estimates from female rats in the study by Brunner et al. (1996) as derived by USEPA (1996). The predicted Aroclor 1268 CSFs are based on Aroclor 1268 TEQs of 2.6 (Hong et al., 1993) and 0.61 (van den Berg et al., 1998) and equal [(Aroclor 1268 TEQ ÷ mixture TEQ) × CSF for the mixture]. As TEQs reported by Ahlborg et al. (1994) are very similar to those of van den Berg et al. (1998), CSF derivation using TEQs reported by Ahlborg et al. is not shown.

3.2. Prediction of an Aroclor 1268 slope factor assuming that an Ah-receptor-independent mechanism exists in addition to an Ah-receptor-dependent mechanism

The second extrapolation approach, like the first, assumes a linear relationship between TEQ and cancer potency in female rats, but does not assume that the cancer potency of an Aroclor mixture becomes zero when its TEQ is zero. In essence, this second extrapolation approach assumes that two mechanisms of cancer induction exist in females (Brown et al., 2001), whereas the first extrapolation approach assumes that TEQ is the sole determinant of cancer potency. In this second approach to CSF estimation, the USEPA-derived CSFs for the PCB mixtures in the Brunner et al. (1996) study (Aroclors 1242, 1254, and 1260, with and without Aroclor 1016) were linearly regressed against their respective TEQs. The CSFs and TEQs used in this regression are those provided in Table 6. The resulting regression equations were then used to predict central tendency and upper-bound CSFs for Aroclor 1268 using a TEQ of 0.68 for this mixture, as discussed above. Regressing the central tendency CSFs for the female rat tumor responses to Aroclors 1242, 1254, and 1260 against their corresponding TEQs as reported by Mayes and co-workers resulted in a linear regression line with the equation: $y = 0.021x + 0.192$, where y is the central tendency CSF (dependent variable) and x is TEQ (independent variable). When the estimated TEQ for Aroclor 1268 of 0.68 is substituted into this equation, a central tendency CSF of 0.21 (mg/kg-day)$^{-1}$ is derived. This same process was used to predict an upper-bound CSF for Aroclor 1268 of 0.27 (mg/kg-day)$^{-1}$. As was done for the first extrapolation approach using comparative TEQ analysis, central and upper-bound CSFs for Aroclor 1268 based on TEQs published by Hong et al. (1993) and van den Berg et al. (1998) were also estimated and proved to be comparable to those estimated using the Mayes' data (data not shown). Table 8 presents the regression equations and the central and upper-bound CSFs that were estimated from the Mayes' data set (i.e., 0.21 and 0.27 (mg/kg-day)$^{-1}$ for central and upper-bound CSFs, respectively). Table 8 also shows the linear regression equations and slope factor estimates for Aroclor 1268 when the data for all four tested Aroclors (1016, 1242, 1254, and 1260) are included. In this case, inclusion of Aroclor 1016 data did not greatly skew the linear relationship observed across the three higher TEQ Aroclor mixtures. In fact, the correlation coefficients were consistently above 0.98 for each of the four regression lines presented in Table 8. However, inclusion of the Aroclor 1016 data leads to estimated Aroclor 1268 slope factors about 25–30% lower than those predicted using the higher TEQ Aroclor mixture data alone.

As can be seen by comparing the analyses in Tables 6 and 8 (exclusive of Aroclor 1016, the inclusion of which results in seemingly anomalous slope factor estimates), CSF estimates for Aroclor 1268 were different for the two extrapolation approaches, as the linear regression method yielded values 7- to 8-fold higher than those derived by assuming that the CSF was directly proportional to the mixture TEQ. In other words, when two cancer mechanisms are assumed to co-exist in females, that mechanism independent of the Ah-receptor contributes more to the value of the Aroclor 1268 CSF than does the mechanism mediated by the Ah-receptor. In fact, for Aroclors 1016, 1242, 1254, 1260, and 1268, the

Table 8
Predicted cancer slope factors for Aroclor 1268 based on linear regression analysis of Aroclor TEQ vs. slope factors

Aroclors included	Regression equation (central estimate)	Correlation coefficient (r)	Regression equation (upper-bound)	Correlation coefficient (r)	Central cancer slope factor	Upper-bound cancer slope factor
Only Aroclors 1242, 1254, and 1260	$y = 0.021x + 0.192$	0.993	$y = 0.026x + 0.254$	0.995	0.21	0.27
Aroclors 1016, 1242, 1254, and 1260	$y = 0.023x + 0.126$	0.987	$y = 0.028x + 0.175$	0.988	0.14	0.20

Linear regression equations describe best fit lines through data points consisting of central or upper-bound CSFs for female rat tumor responses to Aroclors 1242, 1254, and 1260, with or without Aroclor 1016, regressed against their respective mixture TEQs as cited in Brunner et al., 1996 and Mayes et al., 1998. In the above regression equations, y is the central or upper-bound CSF and x is the estimated Aroclor 1268 TEQ of 0.68. Cancer slope factors were obtained by simply substituting 0.68 for x in the regression equations and solving for y.

non-Ah-receptor mechanism is estimated to contribute 100%, 44–64%, 12–17%, 35–51%, and 88–94% of the upper-bound CSF value, respectively (the contribution of the non-Ah-receptor mechanism can be estimated by assigning a value of zero to x in the regression equations in Table 8). These percentages are roughly inversely related to the combined percentages of tetra-, penta-, and hexachlorobiphenyls found in these PCB mixtures (Aroclor 1016: 34%; Aroclor 1242: 45%; Aroclor 1254: 93%; Aroclor 1260: 56%; Aroclor 1268: 5%), an observation that also correlates with the abundance of the more potent 'dioxin-like' PCBs and PCDFs in these mixtures. The contribution of the Ah-receptor mediated mechanism to the CSF is, as would be predicted, maximal for the most potent Aroclor (i.e., Aroclor 1254) and minimal for the mixtures which are arguably the least potent based on TEQ content (i.e., Aroclors 1016 and 1268). Interestingly, using a rat liver tumor promotion model van der Plas et al. (2000) have calculated that 80% of the total liver tumor promoting capacity of Aroclor 1260 resides with its non-dioxin-like fraction. Given the high percentage contribution of the non-Ah-receptor mechanism to the potency of Aroclor 1268 in females, one might predict that the CSF for Aroclor 1268 in male rats, the sex for which cancer potency does not correlate with TEQ content, would be more comparable than that of the other Aroclors to the CSF for female rats. As shown in the next analysis, this non-Ah-receptor mediated response in male animals is quite comparable to the response in females when both non-Ah-receptor and Ah-receptor mechanisms are assumed to co-exist.

3.3. Prediction of an Aroclor 1268 slope factor for male rats assuming a mechanism related to the bioaccumulation potential of PCB mixtures

Factors that dictate PCB potency for the mechanism of hepatocarcinogenesis predominant in male rats remain unidentified, but it appears unlikely at present that the mechanism involves the Ah-receptor. A possible Ah-receptor-independent mechanism operative in males is a hepatic response to the bioaccumulation of those PCB congeners most resistant to metabolic clearance. Indeed, Brown and colleagues (Silkworth et al., 1997) have speculated that the carcinogenic potency of a PCB mixture in male rats is a function of its bioaccumulation potential. If this is the case, then the cancer potency of Aroclor 1268 might be expected to be similar to (or perhaps slightly greater than) that of Aroclor 1260. To estimate Aroclor 1268 cancer potency based on male rat tumor responses, with the assumption that potency is a function of bioaccumulation potential, a regression approach was utilized. Similar to the regressions of CSF versus TEQ content in females, USEPA-derived cancer potency values for Aroclors 1016, 1242, 1254, and 1260 from the Brunner et al. (1996) study were used (USEPA, 1996). Unfortunately, there is no unambiguous parameter

Table 9
Predicted cancer slope factors for Aroclor 1268 based on linear regression analysis

Variables regressed	Regression equation	Correlation coefficient (r)	Cancer slope factor $(mg/kg\text{-}day)^{-1}$
Upper-bound CSF vs. average No. of Cl atoms per biphenyl molecule	$y = 0.0430x - 0.0879$	0.946	0.27
Central tendency CSF vs. average No. of Cl atoms per biphenyl molecule	$y = 0.0239x - 0.0546$	0.994	0.14
Upper-bound CSF vs. percentage chlorine by weight	$y = 0.0066x - 0.2214$	0.904	0.23
Central tendency CSF vs. percentage chlorine by weight	$y = 0.0038x - 0.1336$	0.976	0.12

Linear regression equations describe best fit lines through data points consisting of central or upper-bound CSFs of Aroclors 1016, 1242, 1254, and 1260 (for male rats in Brunner et al., 1996) regressed against their respective average number of chlorine atoms per biphenyl molecule (estimated based on Table 3 to be 3.13, 3.43, 5.02, and 6.35 for Aroclors 1016, 1242, 1254, and 1260, respectively) or their respective percentages of chlorine by weight (1, 42, 54, and 60%, respectively). In the above regression equations, y is the central or upper-bound CSF and x is 8.31 (the average number of chlorine atoms per biphenyl molecule composing Aroclor 1268) or 68 (the percentage chlorine by weight of Aroclor 1268). Cancer slope factors were obtained by simply substituting 8.31 or 68 for x in the appropriate regression equations and solving for y.

for the bioaccumulation potential of all PCB mixtures and, as a result, two indirect indicators of bioaccumulation potential were used in the regressions—percentage chlorine content by weight and average number of chlorine atoms per molecule. These two indicators correlate with one another to some degree, but each has different implications with respect to congener distribution, bioaccumulation potential and mixture toxicity. The regression equations are summarized in Table 9.

From these regression equations, CSF estimates were derived for Aroclor 1268 based on its percentage chlorine content by weight and average number of chlorines per biphenyl molecule. As shown in Table 9, central tendency slope factor estimates for Aroclor 1268 based on the two regression lines were 0.14 and 0.12 $(mg/kg\text{-}day)^{-1}$, while upper-bound estimates were 0.27 and 0.23 $(mg/kg\text{-}day)^{-1}$. These values are quite similar to the CSF estimates for Aroclor 1268 derived from data on female rats using the linear regression approach when the value of x (i.e., the Ah-receptor mediated component) is set to zero (see Table 8). When this is done, the central tendency and upper-bound CSF estimates for female rats due to the non-Ah-receptor mediated component are estimated to be about 0.19 and 0.25 $(mg/kg\text{-}day)^{-1}$, respectively, based on the higher TEQ mixtures (exclusive of Aroclor 1016), and about 0.13 and 0.18 $(mg/kg\text{-}day)^{-1}$ based on all four Aroclor mixtures. The similarity in the CSFs derived for the non-Ah-receptor mediated component of both sexes suggests that the bioaccumulation mechanism thought to be operative in males may be the second mechanism observed to occur in female rats. If this is indeed the case, the results of chronic cancer bioassays of Aroclor 1268 would likely resemble the responses of male rats in the Brunner et al. (1996) study rather than the generally greater response of female rats.

The two indirect indicators of bioaccumulation potential (i.e., percentage chlorine content by weight and average number of chlorine atoms per molecule) were also regressed against empirical data describing the relative accumulation of total adipose PCBs in rats following treatment with Aroclors 1016, 1242, 1254, and 1260 (relative accumulation = 0.04, 0.05, 0.51, and 1, respectively) (Silkworth et al., 1997). From the resulting linear regression equations, the relative accumulation of Aroclor 1268 was estimated to be 1.52 which represents the mean of the two estimates that were made using the two indirect indicators of bioaccumulation potential (i.e., 1.73 and 1.30). Regression equations were then derived for the prediction of central tendency and upper-bound CSFs based on bioaccumulation potential from which CSFs for Aroclor 1268 were estimated (see Table 10). These CSFs of 0.26 (upper-bound) and 0.14 (central tendency) are very similar to the respective average of the two values (averaging 0.25 and 0.13) predicted in Table 9 using indirect indicators of bioaccumulation potential rather than empirical data.

With regard to the above analyses based on bioaccumulation potential, it is noteworthy that only Aroclor 1260 was found to be carcinogenic for male rats in the Brunner et al. (1996) study, although cancer potency estimates for other Aroclor mixtures (Aroclors 1016, 1242, and 1254) were mathematically estimated by the USEPA based on the study's sensitivity. While Aroclor 1260 has greater chlorination and hence a greater bioaccumulation potential than the other Aroclors tested in the Brunner et al. (1996) study, other differences exist among the Aroclors that could also explain the observed differences in cancer potency. It is certainly possible for example, that the presence of certain individual PCB congeners may be necessary for carcinogenicity and that the pattern of chlorination is as important, if not more important, than the overall degree of chlorination. Despite the fact that a rigorous examination of the relationship between chlorination (or bioaccumulation) and cancer potency is precluded by the fact that only one of the four PCB mixtures in the Brunner et al. (1996) study was positive for carcinogenicity in males, if it is assumed that a bioaccumulation-related mechanism exists and is a function of chlorine content, available data predict central tendency and upper-bound CSFs for Aroclor 1268 in males of 0.12 to 0.14 and 0.23 to 0.27 $(mg/kg\text{-}day)^{-1}$, respectively (see Tables 9 and 10). These values are remarkably similar to the estimates for the "non-Ah-receptor mediated" cancer potency of PCBs in females when TEQs are set at zero. This in turn suggests that because Aroclor 1268 has a very low TEQ value, the

Table 10
Predicted cancer slope factors for Aroclor 1268 based on linear regression analysis

Variables regressed	Regression equation	Correlation coefficient (r)	Cancer slope factor $(mg/kg\text{-}day)^{-1}$
Upper-bound CSF vs. relative bioaccumulation of total adipose PCBs	$y = 0.1419x + 0.0482$	0.951	0.26
Central CSF vs. relative bioaccumulation of total adipose PCBs	$y = 0.0783x + 0.0212$	0.994	0.14

Linear regression equations describe best fit lines through data points consisting of central or upper-bound CSFs of Aroclors 1016, 1242, 1254, and 1260 (for male rats in Brunner et al., 1996) regressed against the relative accumulation of total adipose PCBs for the respective Aroclor mixtures (Silkworth et al., 1997). In the above regression equations, y is the central or upper-bound CSF and x is the relative accumulation of total adipose PCBs. Cancer slope factors for Aroclor 1268 were obtained by simply substituting 1.52 (the estimated relative bioaccumulation potential of Aroclor 1268) for x in the appropriate regression equation and solving for y.

large sex difference observed with the more moderately chlorinated mixtures (i.e., Aroclors 1242, 1254, and 1260) would essentially be absent, much like that observed for Aroclor 1016, which has a similarly low TEQ content relative to the other mixtures assessed directly for cancer potency.

3.4. Estimation of the Ah-receptor mediated component in Aroclor 1268 after correcting for the contribution to potency made by the Ah-receptor-independent component

Because the carcinogenic potency of PCB mixtures in female animals is derived from two sources, i.e., Ah-receptor-dependent and Ah-receptor-independent mechanisms, the most representative estimate of the Ah-receptor-dependent contribution to Aroclor 1268's potency is made after correcting for the contribution made by the Ah-receptor-independent mechanism. This correction was not made in the calculations provided in Table 6 since the effect of the Ah-receptor-independent mechanism had not yet been estimated for either sex. The regression equations in Table 8 (with and without Aroclor 1016) indicate that the Ah-receptor-independent mechanism (which is probably linked to bioaccumulation) contributes 0.126–0.192 (central tendency) and 0.175–0.254 (upper-bound) $(mg/kg\text{-}day)^{-1}$ to the final CSF estimates for female rats when two mechanisms are assumed to co-exist. Subtracting the average of these central tendency ($0.159\,(mg/kg\text{-}day)^{-1}$) and upper-bound ($0.215\,(mg/kg\text{-}day)^{-1}$) contributions from the CSFs for each Aroclor before using them to predict a CSF for Aroclor 1268 should provide a more representative estimate of the Ah-receptor mediated cancer potency of Aroclor 1268. By repeating the calculations originally made in Table 6 after correcting for the non-Ah-receptor contribution, revised CSF estimates for Aroclor 1268 were derived (see Table 11). All of the predicted CSFs for Aroclor 1268 in Table 11 were comparable to those derived in Table 6 for Aroclor 1268 based on the mixture TEQ and CSF of Aroclor 1254 (i.e., 0.017 and 0.021 $(mg/kg\text{-}day)^{-1}$ for central tendency and upper-bound, respectively). This result was anticipated as the total cancer potency for Aroclor 1254 was the least affected of all the Aroclors by the Ah-receptor-independent mechanism. On the other hand, subtracting the non-Ah-receptor contribution from the Aroclor 1016 CSFs led to negative slope factors for the Ah-receptor-dependent component, and hence corrected CSFs for Aroclor 1016 were not included in the Aroclor 1268 slope factor calculations. These findings further suggest that the low TEQ and low cancer potency of Aroclor 1016 may be best explained by non-Ah-receptor mechanisms or by the absence of any appreciable tumorigenic response in the rat studies of Brunner et al. (1996).

In summary, the original calculations made in Table 6 for the Ah-receptor-dependent fraction of the Aroclor CSF were inflated by the effect of a second, Ah-receptor-independent mechanism. This inflation had its greatest impact on the predicted Aroclor 1268 CSFs derived from Aroclors 1242 and 1260, two PCB mixtures for which this second mechanism appears to contribute about one-half of the observed potency. By correcting for the contribution of this second mechanism, a better estimate of the fraction of Aroclor 1268's cancer potency contributed by the Ah-receptor-dependent mechanism has been derived. This fraction is estimated to be about $0.02\,(mg/kg\text{-}day)^{-1}$ and is quite similar across all of the PCB mixtures in Table 11 (contrast this with the greater variability across predicted Aroclor 1268 CSFs in Table 6). Thus, we have a high degree of confidence in the mean predicted CSFs for Aroclor 1268 in Table 11 (0.017 and $0.020\,(mg/kg\text{-}day)^{-1}$) attributable to the Ah-receptor-dependent fraction of cancer potency.

Table 11
Predicted Ah-receptor-dependent cancer slope factors for Aroclor 1268 after correction for the Ah-receptor-independent mechanism(s)

PCB mixture	Mixture TEQ[b]	Cancer slope factor[a]		Predicted cancer slope factor for Aroclor 1268[c]	
	Mayes et al. (1998)	Corrected central tendency	Corrected upper-bound	Based on central tendency	Based on upper-bound
Aroclor 1260	7.2	0.241	0.285	0.023	0.027
Aroclor 1254	47.6	1.04	1.29	0.015	0.018
Aroclor 1242	7.8	0.141	0.185	0.012	0.016
Aroclor 1016	0.11	(Negative)	(Negative)	–	–
Average ± SD (without Aroclor 1016)				0.017 ± 0.005	0.020 ± 0.006
(SD as percentage of mean)				(33%)	(28%)

[a] Corrected CSFs are in $(mg/kg\text{-}day)^{-1}$ and were derived by subtracting 0.159 or $0.215\,(mg/kg\text{-}day)^{-1}$ from those CSFs reported for female rats in USEPA (1996).

[b] The TEQ values listed in this column are those reported for the Brunner et al. (1996) study in the recent publication of this experiment by Mayes et al. (1998).

[c] The total TEQ for Aroclor 1268 was 1.43% (Hong et al., 1993; van den Berg et al., 1998) that for Aroclor 1254. Using this percentage (1.43%) and the total TEQ of 47.6 μg/g for Aroclor 1254 as measured in the Brunner et al. (1996) study (Mayes et al., 1998), the projected TEQ for Aroclor 1268 would be 0.68. Predicted CSFs for Aroclor 1268 were arrived at using the formula: [(0.68 ÷ mixture TEQ from Mayes et al. (1998)) × Corrected CSF for the mixture].

4. Summary and conclusions

The analyses presented in this report are consistent with the contemporary concept of two different mechanisms of PCB hepatocarcinogenesis in rats, one Ah-receptor-dependent and the other Ah-receptor independent (Brown et al., 2001). Data from Brunner et al. (1996) and other studies suggest that the Ah-receptor-dependent mechanism exists predominantly in female rats, and that at least a second mechanism, one that is Ah-receptor independent, is present in both male and female rats. The presence of an Ah-receptor-dependent mechanism in females would explain their generally greater sensitivity to PCB hepatocarcinogenesis compared with males, and the close correlation in females (but not males) between cancer potency and the TEQ content of the PCB mixture being tested (at least for the moderately chlorinated mixtures). Because of this high degree of correlation between cancer potency and TEQ content, it is expected that the subordinate, Ah-receptor-independent mechanism in females would be largely masked by the stronger response mediated by the Ah-receptor for the most commonly used commercial PCB mixtures, and would become apparent only in PCB mixtures with very low TEQ values (such as Aroclors 1016 and 1268). This would explain the positive y-axis intercept in regressions of CSFs versus TEQ values for females and the similarity of male and female CSFs for Aroclor 1268 when both are derived using linear regression analysis.

The coplanar tetra-, penta-, and hexa-chlorinated PCB congeners comprise a relatively small fraction of Aroclor 1268, corresponding to its low TEQ content compared to other heavily chlorinated Aroclors (e.g., 1260 and 1254) that exhibit much higher TEQ content. Accordingly, the more potent and sex-dependent (female rat) tumorigenic response reported for Aroclors 1254 and 1260 would not be expected for Aroclor 1268. Similarly, the lack of a substantial sex-dependent response would also be predicted when the chlorination of the Aroclor mixture is very limited, as it is with Aroclor 1016. For Aroclor 1016, its weak overall Ah-receptor mediated potency combined with the lower potential for its congeners to bioaccumulate would be predicted to produce a lower CSF that has little sex-dependence. This is in fact what was observed in the Brunner et al. (1996) study where the estimated upper-bound CSF for Aroclor 1016 was 0.07 in females and 0.04 in males (USEPA, 1996).

Several CSF estimation approaches for Aroclor 1268 have been examined in the present study. All of these estimation approaches make use of existing data on the cancer potency of other PCB mixtures, predominantly from the recent study by Brunner et al. (1996), coupled with differing assumptions regarding mechanism(s) of PCB hepatocarcinogenesis. All of the estimation approaches when applied to Aroclor 1268 yielded cancer potency estimates that are nearly an order of magnitude or more below the current upper-bound USEPA default value of $2\,(\text{mg/kg-day})^{-1}$. Estimates based solely on relative TEQ content, which recognize the dominant role of the Ah-receptor-dependent mechanism in female rats, are some 60- and 100-fold below the regulatory default values for the central tendency ($1.0\,(\text{mg/kg-day})^{-1}$) and upper-bound slope factors ($2.0\,(\text{mg/kg-day})^{-1}$), respectively (see averages in Table 11). If one assumes, as the data suggest, that the Ah-receptor-dependent mechanism in females is also accompanied by an Ah-receptor-independent mechanism, then the application of linear regression analysis yields CSFs roughly an order of magnitude higher than those estimated based on relative TEQ content alone (see Table 8 versus Table 11). The estimates of the Ah-receptor-independent contribution to cancer potency are similar for both sexes, and are based on the assumption that the chlorine content of a PCB mixture determines its degree of bioaccumulation, which in turn dictates the final cancer potency of the mixture.

Based on the use of comparative TEQ analysis for females and linear regression analysis for both sexes, it seems appropriate to conclude that an upper-bound Aroclor 1268 CSF should fall between 0.03 (67-fold lower than the default value of 2.0) and $0.27\,(\text{mg/kg-day})^{-1}$ (7- to 8-fold lower than the default value of 2.0). We propose that an upper-bound CSF for Aroclor 1268 of $0.27\,(\text{mg/kg-day})^{-1}$ is reasonable based on the available data. Although this CSF would represent about a 7- to 8-fold reduction relative to USEPA's default value, it is still believed to be a conservative estimate based on the animal data. It not only equals the highest upper-bound estimate calculated for male rats (see Table 9), but also equals the highest upper-bound estimate calculated for females assuming that Ah-receptor-dependent and independent cancer mechanisms co-exist (see Table 8).

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