

3. CANCER IN EXPERIMENTAL ANIMALS

In previous evaluations in 1978, 1979, 1987, and 2012 ([IARC, 1978, 1979, 1987, 2012](#)), the Working Group concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of polychlorinated biphenyls (PCBs). New data have since become available, and these have been taken into account in the present evaluation.

3.1 Oral administration

See [Table 3.1](#) and [Table 3.2](#)

3.1.1 Individual PCBs and binary mixtures

The United States National Toxicology Program (NTP) has conducted a series of studies to evaluate the carcinogenicity of some PCB congeners administered alone or as binary mixtures in female Harlan Sprague-Dawley rats treated by gavage.

(a) PCB-126

Rat

Groups of 81 female Harlan Sprague-Dawley rats (age, 8 weeks) were given the dioxin-like congener PCB-126 at a dose of 0 (vehicle control), 30, 100, 175, 300, 550, or 1000 ng/kg body weight (bw) by gavage in corn oil : acetone (99 : 1), 5 days per week, for up to 104 weeks (core study) ([Brix et al., 2004](#); [Nyska et al., 2004](#); [Walker et al., 2005](#); [Yoshizawa et al., 2005, 2007, 2009](#); [NTP, 2006a](#)). Ten rats per group were evaluated at 14, 31, or 53 weeks. A stop-exposure group of 50 female rats was given PCB-126 at a dose of 1000 ng/kg bw in corn oil : acetone (99 : 1) by gavage for 30 weeks, then the vehicle only for the remainder of

the study. There were treatment-related increases in the incidences of cholangiocarcinoma and hepatocellular adenoma in rats treated with PCB-126 at doses of 300 ng/kg bw or higher, and 550 ng/kg bw or higher, respectively, for up to 104 weeks. There were three hepatocholangiomas in the group at 1000 ng/kg bw, and single incidences of cholangioma in the groups at 550 and 1000 ng/kg bw. [These tumours are rare, and it was uncertain whether they were related to treatment.] There were also statistically significant, dose-related increases in the incidences of a spectrum of non-neoplastic lesions that collectively were diagnosed as toxic hepatopathy. Significant increases in the incidence of cystic keratinizing epithelioma of the lung occurred in rats at 550 ng/kg bw or higher, and non-statistically significant low incidences of squamous cell carcinoma of the lung were also observed at the highest doses in the core-study groups. Gingival squamous cell carcinomas were observed in all exposure groups, and incidence was significantly increased in the group at 1000 ng/kg bw (core study). Adenomas and/or carcinomas were present in the adrenal cortex of rats in most groups, including the stop-exposure group, with a positive trend in the incidence of adenoma or carcinoma (combined) with increasing dose.

Table 3.1 Studies of carcinogenicity in rats exposed to PCBs and related compounds

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
<i>Individual PCBs and binary mixtures</i>				
Harlan Sprague- Dawley (F) 104 wk NTP (2006a)	Core study: PCB-126 in corn oil : acetone (99 : 1) by gavage at doses of 0, 30, 100, 175, 300, 550, or 1000 ng/kg bw, 5 days/wk, for 104 wk 81 rats/group Stop-exposure study: PCB-126 at 1000 ng/kg for 30 wk followed by vehicle for the remainder of the study 50/group Interim evaluations: 10 rats per core study group were evaluated at wks 14, 31, and 53	<i>Liver</i> Cholangiocarcinoma (includes multiple): 0/53, 0/55, 1/53, 0/53, 5/53, 6/51, 22/53; 0/53, 2/50 (stop-exposure) Multiple: 0/53, 0/55, 0/53, 0/53, 4/51, 15/53; 0/53, 0/50 (stop-exposure) Hepatocellular adenoma ^a (includes multiple): 1/53, 2/55, 1/53, 0/53, 2/53, 4/51, 7/53; 1/53, 0/50 (stop-exposure) Multiple: 0/53, 0/55, 0/53, 0/53, 0/51, 1/53; 0/53, 0/50 (stop-exposure) Hepatocholangioma ^b (includes multiple): 0/53, 0/55, 0/53, 0/53, 0/51, 3/53; 0/53, 0/50 (stop-exposure) Multiple: 0/53, 0/55, 0/53, 0/53, 0/51, 1/53; 0/53, 0/50 (stop-exposure) Cholangioma ^b : 0/53, 0/55, 0/53, 0/53, 1/51, 1/53; 0/53, 0/50 (stop-exposure)	<i>Liver</i> : toxic hepatopathy that included hepatocyte hypertrophy and hyperplasia, bile duct and oval cell hyperplasia, nodular hyperplasia, cholangiofibrosis, multinucleated hepatocytes, diffuse fatty change, bile duct cyst, necrosis, pigmentation, inflammation, portal fibrosis <i>Lung</i> : squamous metaplasia, and bronchiolar metaplasia of the alveolar epithelium No tumours were observed at interim evaluations at wk 14 and 31	
			$P < 0.001$ (1000 ng/kg bw) $P < 0.001$ (trend) $P \leq 0.001$ (1000 ng/kg bw) $P = 0.033$ (1000 ng/kg bw) $P < 0.001$ (trend) $P < 0.001$ (trend) NS NS $*P < 0.001$ $**P = 0.002$ $P < 0.001$ (trend) $*P \leq 0.001$ NS	Purity, 99% The overall incidence values are presented, but statistical analyses are based on the poly 3 test used by NTP that takes survival differences into account <i>Non-neoplastic lesions</i>
		<i>Lung</i> Cystic keratinizing epithelioma (includes multiple): 0/53, 0/55, 0/53, 0/53, 1/53, 11/51 ^{**} , 35/51 [*] ; 0/53, 0/50 (stop-exposure) Multiple: 0/53, 0/55, 0/53, 0/53, 8/51 [*] , 30/51 [*] ; 0/53, 0/50 (stop-exposure) Squamous cell carcinoma: 0/53, 0/55, 0/53, 0/53, 1/51, 2/51; 0/53, 0/50 (stop-exposure)		

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague- Dawley (F) 104 wk NTP (2006a) (cont.)		<i>Oral mucosa</i> Gingival squamous cell carcinoma: 0/53, 1/55, 1/53, 1/53, 2/53, 2/53, 7/53*; 0/53, 2/50 (stop-exposure) <i>Adrenal cortex</i> Adenoma: 0/52, 1/55, 1/53, 0/53, 0/53, 1/52, 2/53; 0/52, 2/50 (stop-exposure) Carcinoma: 0/52, 1/55, 0/53, 0/53, 1/53, 0/52, 2/53; 0/52, 1/50 (stop-exposure) Adenoma or carcinoma (combined): 0/52, 2/55, 1/53, 0/53, 1/53, 1/52, 4/53; 0/52, 3/50 (stop-exposure)	* $P = 0.010$ $P < 0.001$ (trend) NS NS $P = 0.022$ (trend)	
Harlan Sprague- Dawley (F) 105 wk NTP (2006b)	Core study: PCB-153 in corn oil : acetone (99 : 1) by gavage at doses of 0, 10, 100, 300, 1000 or 3000 µg/kg bw by gavage, 5 days/wk for 105 wk 80–82 rats/group Stop-exposure study: 3000 µg/kg bw for 30 wk followed by vehicle for the remainder of the study 50/group Interim evaluations: 10 rats per core study group were evaluated at 14, 31, and 53 wk	<i>Liver</i> Cholangioma: 0/53, 0/54, 0/53, 0/53, 2/53, 0/51; 0/53, 2/50 (stop-exposure) Hepatocellular adenoma: 0/53, 0/54, 0/53, 0/53, 0/53, 1/51; 0/53, 0/50 (stop-exposure) <i>Thyroid gland</i> Follicular cell adenoma: 0/51, 0/52, 0/53, 0/53, 0/53, 0/51; 0/51, 2/49 (stop-exposure) <i>Interim evaluation (wk 53)</i> <i>Thyroid gland</i> Follicular cell adenoma: 0/10, 0/10, 1/10, 0/10, 0/10, 0/10	NS NS NS NS	Purity, 99% <i>Non-neoplastic lesions</i> Liver: hepatocyte hypertrophy, bile duct hyperplasia, oval cell hyperplasia, fatty change and pigmentation Thyroid gland: follicular cell hypertrophy Ovary and oviduct: chronic active inflammation Uterus: suppurative inflammation No tumours were observed at 14 and 31 wk

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague- Dawley (F) 105 wk NTP (2010) (cont.)		Squamous cell carcinoma: 0/52, 0/52, 3/52, 1/52, 1/52, 0/52; 0/52, 1/50 (stop exposure) <i>Pancreas</i> Acinar adenoma: 0/52, 0/52, 0/52, 2/52, 3/52, 1/47; 0/52, 0/49 (stop-exposure) Acinar adenoma or carcinoma (combined): 0/52, 0/52, 0/52, 2/52, 3/52, 2/47; 0/52, 0/49 (stop exposure) <i>Interim evaluation (wk 53)</i> <i>Liver</i> Cholangiocarcinoma (includes multiple): 0/8, 0/8, 0/10, 0/8, 0/8, 3/8 Hepatocellular adenoma: 0/8, 0/8 0/10, 0/8, 0/8, 1/8	NS NS NS	Pancreas: acinus, cytoplasmic vacuolization Nose: inflammation Kidney: pigmentation No tumours were observed at interim evaluations at wk 14 and 31.
Harlan Sprague- Dawley (F) 105 wk NTP (2006c)	<i>Constant-ratio study:</i> PCB-126 and PCB-153 as binary mixture with PCB-126 at doses of 0, 10, 100, 300, 1000 ng/kg bw per day, and PCB-153 at 0, 10, 100, 300, 1000 µg/kg bw per day in corn oil : acetone (99 : 1) by gavage <i>Varying-ratio study:</i> PCB-126 and PCB-153 as binary mixture at doses of PCB-126 at 300, 300, 300 ng/kg bw per day, and PCB-153 at 100, 300, 1000 µg/kg bw per day by gavage in corn oil : acetone 80–81/group <i>Interim evaluations:</i> 10 rats per core-study group were evaluated at wk 14, 31, and 53	<i>Constant-ratio study:</i> <i>Liver</i> Hepatocellular adenoma: 0/53, 0/53, 3/52, 5/52, 27/51* Multiple: 0/53, 0/53, 0/52, 0/52, 16/51* Hepatocellular carcinoma: 0/53, 0/53, 0/52, 0/52, 2/51 Cholangiocarcinoma: 0/53, 0/53, 1/52, 9/52*, 30/51** Multiple: 0/53, 0/53, 1/52, 5/53*, 21/52** Hepatocellular carcinoma: 0/53, 0/53, 0/52, 2/52, 6/51* Multiple: 0/53, 0/53, 0/52, 0/52, 16/51*	* $P < 0.001$ $P < 0.001$ (trend) * $P \leq 0.01$ NS * $P \leq 0.05$ ** $P \leq 0.01$ * $P \leq 0.05$ ** $P \leq 0.01$ $P \leq 0.001$ (trend) * $P = 0.012$ $P \leq 0.001$ (trend) * $P \leq 0.01$	Purity, > 99% (PCB-126 and PCB-153) <i>Non-neoplastic lesions</i> Liver: toxic hepatopathy that included hepatocyte hypertrophy and hyperplasia, bile duct and oval cell hyperplasia, nodular hyperplasia, cholangiofibrosis, multinucleated hepatocytes, diffuse fatty change bile duct cyst, necrosis, pigmentation, inflammation, portal fibrosis Lung: alveolar epithelium, metaplasia; bronchiolar epithelium, squamous metaplasia Adrenal cortex: atrophy and hyperplasia Thyroid gland: follicular cell hypertrophy Oral mucosa: gingival squamous hyperplasia

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague- Dawley (F) 105 wk NTP (2006c) (cont.)		<i>Lung</i> Cystic keratinizing epithelioma: 0/53, 0/53, 0/52, 1/53, 11/52* Multiple: 0/53, 0/53, 0/52, 0/53, 8/52* Squamous cell carcinoma: 0/53, 0/53, 0/52, 1/53, 1/52 <i>Oral mucosa</i> Squamous cell carcinoma: 0/53, 0/53, 2/53*, 5/53, 9/53**	* $P < 0.001$ $P < 0.001$ (trend) * $P \leq 0.01$ NS * $P = 0.031$ ** $P = 0.002$ $P < 0.001$ (trend)	
		<i>Pancreas, acinus</i> Adenoma: 0/53, 1/53, 1/52, 3/52, 1/50 Adenoma or carcinoma (combined): 0/53, 1/53, 1/52, 4/52, 2/50 <i>Uterus</i> Squamous cell carcinoma*: 1/53, 1/53, 1/53, 4/53, 0/53 <i>Adrenal cortex</i> Adenoma: 0/53, 0/53, 0/52, 1/52, 1/51	NS NS NS NS	Pancreas acinus atrophy and cytoplasmic vacuolization
		<i>Varying-ratio study:</i> <i>Liver</i> Hepatocellular adenoma: 2/50, 5/52, 21/51 Multiple: 2/50, 0/52, 7/51 Cholangiocarcinoma: 7/50, 9/52, 25/51 Multiple: 1/50, 5/52, 13/51 Hepatocarcinoma: 0/53, 0/50, 2/52, 2/51	$P \leq 0.001$ NR $P \leq 0.001$ NR NR	For the varying-ratio study, note that P values represent a trend test across the three groups of PCB-126/PCB-153 mixtures and indicated the significance of the effect of increasing the proportion of PCB-153 in the mixture

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague- Dawley (F) 104 wk NTP (2006d)	<i>Core study:</i> PCB-126 and PCB-118 by gavage as binary mixture at doses of PCB-126 at 0, 62, 187, 622, 1866 or 3110 ng/kg bw per day, and PCB-118 at 0, 10, 30, 100, 300 or 500 µg/kg bw per day, in corn oil : acetone (99 : 1). [0, 7, 22, 72, 216 or 360 ng TEQ/ kg bw] <i>Stop-exposure study:</i> PCB-126/PCB-118 at 3110 ng//500 µg/kg bw for 30 wk and then vehicle only for the remainder of the study. 81–86/group <i>Interim evaluations:</i> 10 rats per core study group were evaluated at 14, 31 and 53 wk	<i>Liver</i> Cholangiocarcinoma: 0/53, 0/51, 5/53, 19/53, 28/53, 12/65; 0/53, 19/50 (stop exposure) Multiple: 0/53, 0/51, 1/53, 12/53, 21/53, 72/65; 0/53, 12/50 (stop-exposure) Hepatocellular adenoma: 2/53, 1/51, 0/53, 4/53, 17/53, 5/65; 2/53, 1/50 (stop exposure) Multiple: 0/53, 0/51, 0/53, 2/53, 10/53, 2/65; 0/53, 0/50 (stop exposure) Hepatocellular carcinoma: 0/53, 0/51, 0/53, 0/53, 1/53, 0/65; 0/53, 0/50 (stop exposure) Hepatocholangioma: 0/53, 0/51, 0/53, 1/53, 1/53, 1/65; 0/53, 1/50 (stop exposure) Cholangioma: 0/53, 0/51, 0/53, 1/53, 0/53, 0/65; 0/53, 0/50 (stop exposure) <i>Lung</i> Cystic keratinizing epithelioma: 0/53, 0/51, 0/53, 20/53, 49/53, 41/66; 0/53, 12/50 (stop-exposure)	$P < 0.001$ (≥ 72 ng TEQ), $P < 0.001$ (trend) $P < 0.001$ (stop- exposure) $P \leq 0.05$ (≥ 72 ng TEQ) $P < 0.001$ (216 ng), $P = 0.021$ (360 ng) $P < 0.001$ (trend) $P \leq 0.001$ (216 ng) NS NS NS $P < 0.001$ (≥ 72 ng TEQ), $P < 0.001$ (trend) $P < 0.001$ (stop- exposure) $P \leq 0.01$ (≥ 72 ng TEQ) $P \leq 0.05$ (stop- exposure)	PCB-118, purity, > 98.5% (0.6% PCB-126; 0.2% PCB-77; 0.55% PCB-167) No animals in the core-study groups receiving the two higher doses survived to the end of the study, and survival in the stop-exposure group was significantly lower than in the vehicle- control group. Mean body weights in groups receiving PCB-126/PCB-118 at 622 ng/100 µg/kg bw or more were lower than in the vehicle-control groups throughout most of the study <i>Non-neoplastic lesions</i> Liver: the spectrum and severity of effects at the interim and 2-year time-points increased with dose and duration of exposure. At the end of the study in all groups receiving PCBs, there were significantly increased incidences and severity of toxic hepatopathy characterized by hepatocyte hypertrophy, multinucleated hepatocytes, pigmentation, diffuse fatty change, nodular hyperplasia, centrilobular fibrosis, cholangiofibrosis, oval cell hyperplasia, bile duct cyst, bile duct hyperplasia, and portal fibrosis

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
CR Sprague- Dawley (M, F) 24 mo Maves et al. (1998) , Farooni et al. (2001) , Brown et al. (2007) (cont.)		<i>Liver (F)</i> <i>Aroclor 1016:</i> Hepatocellular adenoma: 1/100, 1/50, 5/50*, 5/50* Multiple: 0/100, 0/50, 1/50, 3/50 Hepatocellular carcinoma: 0/100, 0/50, 1/50, 0/50 Total liver tumours: 1/100, 1/50, 6/50*, 5/50**	* $P \leq 0.05$ $P \leq 0.05$ (trend) NS * $P \leq 0.01$ ** $P \leq 0.05$	
		<i>Aroclor 1242:</i> Hepatocellular adenoma: 1/100, 10/50*, 12/50* Multiple: 0/100, 3/50*, 7/50**	* $P \leq 0.01$ * $P \leq 0.05$ ** $P \leq 0.01$	
		Hepatocellular carcinoma: 0/100, 0/50, 2/50 Hepatocholeangioma: 0/100, 1/50, 2/50 Hepatocholeangiocarcinoma: 0/100, 1/50, 0/50 Total liver tumours: 1/100, 11/50*, 15/50*	NS NS NS * $P \leq 0.01$	
		<i>Aroclor 1254:</i> Hepatocellular adenoma: 1/100, 18/50*, 26/50*, 27/50* Multiple: 0/100, 9/50*, 15/50*, 21/50* Hepatocellular carcinoma: 0/100, 0/50, 4/50*, 6/50** Multiple: 0/100, 0/50, 1/50, 4/50*	* $P \leq 0.01$ * $P \leq 0.01$ * $P \leq 0.05$ ** $P < 0.01$ * $P \leq 0.05$	

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
CR Sprague- Dawley (M, F) 24 mo Mayes et al. (1998) , Faroon et al. (2001) , Brown et al. (2007) (cont.)		Hepatocellular carcinoma: 0/100, 2/50, 6/50*, 1/50 Total liver tumours: 1/100, 19/50*, 28/50*, 28/50* <i>Aroclor 1260</i> : Hepatocellular adenoma: 1/100, 9/50*, 10/50*, 21/50* Multiple: 0/100, 6/50*, 8/50*, 16/50* Hepatocellular carcinoma: 0/100, 1/50, 1/50, 5/50* Multiple: 0/100, 0/50, 0/50, 1/50 Hepatocellular carcinoma: 0/100, 0/50, 0/50, 3/50* Total liver tumours: 1/100, 10/50*, 11/50*, 24/50* <i>Thyroid gland (M)</i> <i>Aroclor 1016</i> : Follicular cell adenoma: 1/100, 3/50, 2/50, 0/50 Follicular cell carcinoma: 1/100, 1/50, 1/50, 1/50 Total thyroid tumours: 2/100, 4/50, 3/50, 1/50 <i>Aroclor 1242</i> : Follicular cell adenoma: 1/100, 5/50*, 5/50* Follicular cell carcinoma: 1/100, 2/50, 1/50 Total thyroid tumours: 2/100, 7/50*, 6/50**	*P ≤ 0.01 *P ≤ 0.01 *P ≤ 0.01 *P ≤ 0.01 *P ≤ 0.01 NS *P ≤ 0.05 *P ≤ 0.01	
			NS	
			*P ≤ 0.05	
			*P ≤ 0.01	
			NS	
			NS	
			NS	
			*P ≤ 0.05	
			NS	
			*P ≤ 0.01 **P ≤ 0.05	

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
CR Sprague- Dawley (M, F) 24 mo Maves et al. (1998) , Farooni et al. (2001) , Brown et al. (2007) (cont.)		<i>Aroclor 1254:</i> Follicular cell adenoma: 1/100, 6/50*, 4/50**, 5/50** Follicular cell carcinoma: 1/100, 1/50, 3/50, 1/50 Total thyroid tumours: 2/100, 7/50*, 7/50*, 6/50** <i>Aroclor 1260:</i> Follicular cell adenoma: 1/100, 6/50*, 4/50*, 3/50 Follicular cell carcinoma: 1/100, 1/50, 1/50, 1/50 Total thyroid tumours: 2/100, 7/50*, 5/50**, 4/50 <i>Mammary gland (F)</i> <i>Aroclor 1254:</i> Fibroadenoma: 34/100, 22/50, 29/50*, 10/50	* $P \leq 0.01$ ** $P \leq 0.05$ NS * $P \leq 0.01$ ** $P \leq 0.05$ * $P \leq 0.01$ NS * $P \leq 0.01$ ** $P \leq 0.05$ * $P \leq 0.01$	
Sprague- Dawley (M, F) 29 mo Norback & Weltman (1985)	Feed containing Aroclor 1260 (mixed with corn oil) at 100 ppm for 16 mo, then at 50 ppm for an additional 8 mo, and then the control diet for an additional 5 mo. Controls received basal diet with added corn oil for 18 mo, then the basal diet only for 10 mo. The medial and left lobes of the liver of 10 rats (2 M and 2 F controls, and 3 M and 3 F PCB-treated rats, for each period) were removed (partial hepatectomy) at 1, 3, 6, 9, 12, 15, and 18 mo Control: 63/group (M, F) Aroclor 1260: 70/group (M, F)	<i>Liver</i> Neoplastic nodule: 0/32, 5/46 (M); 1/49, 2/47 (F) Trabecular carcinoma: 0/32, 2/46 (M); 0/49, 19/47 (F) Adenocarcinoma: 0/32, 0/46 (M); 0/32, 24/47 (F) Cholangioma (simple): 2/32, 14/46 (M); 2/49, 21/47 (F) Cholangioma (cystic): 0/32, 2/46 (M); 1/49, 5/47 (F)	NS $P < 0.0001$ (F) $P < 0.0001$ (F) $P = 0.01$ (M) $P < 0.0001$ (F) NS	Purity, NR Some adenocarcinoma-bearing rats also had trabecular carcinoma (not included in the incidence of trabecular carcinoma) PCB-exposed rats developed hepatocellular lesions in the following sequence: centrilobular cell hypertrophy at 1 mo, foci of cell alteration at 3 mo, areas of cell alteration at 6 mo, neoplastic nodules at 12 mo, trabecular carcinoma at 15 mo, and adenocarcinoma at 24 mo

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Wistar (M) Up to 832 days Schaeffer et al. (1984) , Faroon et al. (2001)	Basic diet for 8 wk, then: Group 1: basic diet; 139 rats (controls) Group 2: basic diet supplemented with Clophen A 30 at 100 ppm; 152 rats Group 3: basic diet supplemented with Clophen A 60 at 100 ppm; 141 rats After 801 days, randomly selected rats from all three groups were killed daily up to day 832	Hepatocellular neoplastic nodules: 5/131, 38/130*, 63/126* Hepatocellular carcinoma: 1/131, 4/130, 61/126* Thymoma: 16/131, 4/130, 2/129 Other neoplasms: 88/131, 66/138, 33/129	* $P < 0.05$ * $P < 0.05$ NS NS	Purity of Clophen A 30, 99.1%; purity of Clophen A 60, 99.9% Over the first 800 days on study, total mortality in groups 2 and 3 was significantly lower than in group 1 (controls) Hepatic foci of cellular alteration were observed in all groups, but were more frequent in the treated groups. There was a trend from foci to neoplastic nodules to hepatocellular carcinoma. Other non-neoplastic hepatic lesions observed in control and treated groups included bile duct hyperplasia The results of a re-evaluation of the hepatocellular tumours using contemporary diagnostic criteria and nomenclature were in general consistent with the original evaluation (Moore et al., 1994) Tumour data were reported in six 100-day periods; the data reflected incidences from day 1 until day 832
Sherman (F) 22 mo Kimbrough et al. (1975) , Moore et al. (1994)	Diets containing Aroclor 1260 at 0 or 100 ppm for up to 21 mo 200/group	<i>Liver</i> Hepatic neoplastic nodules: 0/173, 144/184 Hepatocellular carcinoma: 1/173, 26/184	$P < 0.0001$ $P < 0.0001$	Purity, NR The incidences of the hepatocellular lesions were re-evaluated by a panel of pathologists using contemporary diagnostic criteria and nomenclature (Moore et al., 1994). Lesions that had been previously diagnosed as neoplastic nodules were now classified as either hepatocellular hyperplasia or hepatocellular adenoma. In general, the results were consistent between the original evaluation and the re-evaluation

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Donryu (M, F) ≤ 560 days Kimura & Baba (1973) , Silberhorn et al. (1990)	Diets containing Kanechlor 400 (in olive oil) at 38.5 ppm for 4 wk, then, based on bw-gain, the initial concentration was sequentially increased: 2× for 8 wk 4× for 3 wk 8× for 3 wk 16× for 8 wk, decreased to 12× for 32 wk because bw decreased markedly; two 4-wk periods with no treatment during this time Controls were fed powdered diet mixed with pure olive oil Controls: 5 M + 5 F/group Treated: 10 M + 10 F/group	Liver adenomatous nodules: 0/5, 0/10 (M); 0/5, 6/10 (F) Adrenal gland adenoma: 0/5, 0/10 (M); 0/5, 1/10 (F)	P = 0.044 (F) NS	Purity, NR Multiple small nodules observed in the livers of females, but not males Fatty degeneration observed in the liver of all dosed groups, but only in two females in the control groups Study may have been limited by short duration, small number of rats/group, and may have exceeded the maximum tolerated dose The Working Group noted that current terminology for adenomatous nodules is hepatocellular adenoma

^a Historical controls: 4/371 (1.1% ± 1.5%); range, 0–4%

^b Historical controls: 0/371

^c Historical controls: 4/371 (1.1% ± 1.0%); range, 0–2%

^d Historical controls: 6/473 (1.3% ± 1.4%); range, 0–4%

^e Historical controls: 1/371 (0.3% ± 0.7%); range, 0–2%

bw, body weight; F, female; M, male; mo, month; NR, not reported; NS, not significant; PCB, polychlorinated biphenyl; wk, week; yr, year

Table 3.2 Studies of carcinogenicity in mice exposed to PCBs and related compounds

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence of tumours	Significance	Comments
C57BL/6, B6D2F1 or DBA/2 (M) 44 wk Beebe et al. (1995)	Initiation with a single intraperitoneal dose of NDEA, 90 mg/kg bw, in tricaprylin, or tricaprylin only, and promoted 3 wk later ± Aroclor 1254 (100 ppm) in the diet for 20 wk 18–39/group	<i>Tricaprylin only, or tricaprylin + Aroclor 1254:</i> C57BL/6 mice: Liver tumours (all types): 0/27, 0/27 Lung tumours: 1/27, 1/27 B6D2F1 mice: Liver tumours (all types): 0/31, 2/34 Lung tumours: 0/31, 2/34 DBA/2 mice: Liver tumours (all types): 0/23, 0/24 Lung tumours: 3/31, 1/24	NS NS NS	Purity, NR
dd (M, F) 24 or 32 wk Nagasaki et al. (1975)	Diet containing Kanechlor 300, 400 or 500 for 24 or 32 wk 24-wk study: Kanechlor 400 (0, 100, 250 ppm) or Kanechlor 500 (0, 100, 250 ppm) 32-wk study: Kanechlor 300 (0, 100, 250, 500 ppm) Kanechlor 400 (0, 100, 250, 500 ppm) Kanechlor 500 (0, 100, 250, 500 ppm) 20/group	<i>Hepatocellular carcinoma, 24 wk study:</i> Kanechlor 400: 0/20, 0/20, 0/20 (M) Kanechlor 500: 0/20, 0/20, 0/20 (M) <i>Hepatocellular carcinoma, 32-wk study:</i> Kanechlor 300: 0/20, 0/19, 0/19, 0/20 (M); 0/12, 0/19, 0/20, 0/20 (F) Kanechlor 400: 0/20, 0/17, 0/19, 0/20 (M); 0/12, 0/20, 0/20, 0/17 (F) Kanechlor 500: 0/20, 0/18, 0/20, 9/17*(M); 0/12, 0/19, 0/20, 4/17*(F)	NS NS NS NS *P < 0.05	Purity, NR Other proliferative lesions observed in the liver of mice treated with Kanechlor 400 or 500 included oval cell hyperplasia, bile duct proliferation, cellular hypertrophy and nodular hyperplasia
BALB/cJ (M) 11 mo Kimbrough & Linder (1974) , Faroon et al. (2001)	Diets containing Aroclor 1254 (mixed with corn starch) at 0 or 300 ppm for 6 mo, followed by basal diet for 5 mo, or Aroclor 1254 at 0 or 300 ppm for 11 mo Group 1: control diet for 6 mo Group 2: Aroclor 1254 for 6 mo Group 3: control diet for 11 mo Group 4: Aroclor 1254 for 11 mo 50/group	<i>Hepatoma</i> 6 mo: 0/24, 1/24, 11 mo: 0/34, 10/22	NS P < 0.001	Purity, NR The Working Group noted that “hepatoma” is not a nomenclature currently used in toxicological pathology. In studies before 1978, the term “hepatoma” may have been used to denote benign or malignant liver tumours. In this study it was not clear whether hepatoma referred to a benign or malignant hepatic tumour

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence of tumours	Significance	Comments
dd (M) 32 wk Ito et al. (1973) , Silberhorn et al. (1990) , Faroon et al. (2001)	Basal diet supplemented with Kanechlor for 32 wk: Kanechlor 300 at 0, 100, 250 or 500 ppm Kanechlor 400 at 0, 100, 250 or 500 ppm Kanechlor 500 at 0, 100, 250 or 500 ppm 12 mice/treated group; 6 controls	<i>Liver</i> <i>Kanechlor 300</i> Nodular hyperplasia: 0/6, 0/12, 0/12, 0/12 Hepatocellular carcinoma: 0/6, 0/12, 0/12, 0/12 <i>Kanechlor 400</i> Nodular hyperplasia: 0/6, 0/12, 0/12, 0/12 Hepatocellular carcinoma: 0/6, 0/12, 0/12, 0/12 <i>Kanechlor 500</i> Nodular hyperplasia: 0/6, 0/12, 0/12, 7/12* Hepatocellular carcinoma: 0/6, 0/12, 0/12, 5/12*	NS NS NS NS * $[P < 0.05]$ * $[NS]$	Purity: Kanechlor 300: 59.8% trichlorobiphenyl, 23.0% tetrachlorobiphenyl, 16.6% dichlorobiphenyl, 0.6% pentachlorobiphenyl Kanechlor 400: 43.8% tetrachlorobiphenyl, 32.8% trichlorobiphenyl, 5.8% pentachlorobiphenyl, 4.6% hexachlorobiphenyl, 3.0% dichlorobiphenyl Kanechlor 500: 55.0% pentachlorobiphenyl, 26.5% tetrachlorobiphenyl, 12.8% hexachlorobiphenyl, 5.0% trichlorobiphenyl The description of nodular hyperplasias provided was not sufficiently detailed to determine whether these hyperplastic nodules were benign hepatocellular adenomas according to current nomenclature Other histopathological changes in mice treated with PCBs included oval cell proliferation, bile duct proliferation and hepatocyte hypertrophy. Amyloid deposition was also observed in the livers of mice fed diets containing various commercial PCB mixtures at 100 or 250 ppm

d, day; mo, month; NDEA, *N*-nitrosodiethylamine; NR, not reported; NS, not significant; PCB, polychlorinated biphenyl; wk, week; yr, year

(b) PCB-153**Rat**

Groups of 80–82 female Harlan Sprague-Dawley rats (age, 8 weeks) were given the di-*ortho*-substituted non-dioxin-like congener PCB-153 (purity, 99%) at a dose of 0 (81 rats; vehicle control), 10, 100, 300, 1000, or 3000 µg/kg bw, in corn oil:acetone (99 : 1) by gavage, 5 days per week, for up to 105 weeks (core study) ([Yoshizawa et al., 2005, 2007, 2009](#); [NTP, 2006b](#)). Ten rats per group were evaluated at 14, 31, or 53 weeks. A stop-exposure group of 50 female rats was given PCB-153 at 3000 µg/kg bw corn oil : acetone (99 : 1) by gavage for 30 weeks, and then the vehicle only for the remainder of the study. At 2 years, cholangiomas occurred in two rats at 1000 µg/kg bw and in two rats in the stop-exposure group. A single hepatocellular adenoma was observed in the group at 3000 µg/kg bw. Cholangioma did not occur in the historical vehicle controls (0 out of 371) of the NTP studies. [One factor limiting interpretation of effects in this bioassay was that the highest dose of PCB-153 used (3000 µg/kg bw) was chosen to match the highest dose used in an NTP bioassay with a mixture of PCB-126 and PCB-153 ([NTP, 2006c](#)), rather than on the basis of the results of a previous short-term study of toxicity. There was no effect of PCB-153 at 3000 µg/kg bw on survival or body weight in this 2-year study, suggesting that higher doses would probably have been tolerated. In a tumour-promotion study in F344 female rats, [Dean et al. \(2002\)](#) gave PCB-153 at a dose of 10 000 µg/kg bw by gavage, three times per week, for 8 weeks, and observed only a significant increase in liver weight.]

(c) PCB-118**Rat**

Groups of 80 female Harlan Sprague-Dawley rats (age, 8 weeks) were given PCB-118 (purity, > 99%) at a dose of 0 (vehicle control), 100, 220, 460, 1000, or 4600 µg/kg bw in corn oil : acetone

(99 : 1) by gavage, 5 days per week, for up to 105 weeks (core study) ([Yoshizawa et al., 2009](#); [NTP, 2010](#)). Ten rats per group were evaluated at 14, 31, or 53 weeks. A stop-exposure group of 50 female rats was given PCB-118 at a dose of 4600 µg/kg bw in corn oil : acetone (99 : 1) by gavage for 30 weeks, then the vehicle for the remainder of the study. At the 53-week interim evaluation, three cholangiocarcinomas and one hepatocellular adenoma were observed in the group at 4600 µg/kg bw. At 2 years, the incidences of multiple cholangiocarcinoma, and single or multiple cholangiocarcinoma (combined) in the group at 4600 µg/kg bw and the stop-exposure group were significantly greater than those in the vehicle-control group. The incidences of multiple hepatocellular adenoma in the group at 4600 µg/kg bw, and single or multiple hepatocellular adenoma (combined) in the groups at 1000 µg/kg bw or 4600 µg/kg bw were significantly greater than those in the vehicle-control group. Four rats developed hepatocholangioma and one rat developed hepatocellular carcinoma in the group at 4600 µg/kg bw. Significantly increased incidences of multiple cystic keratinizing epithelioma of the lung and of single or multiple cystic keratinizing epithelioma (combined) occurred in the group at 4600 µg/kg bw compared with the vehicle-control group. The incidence of uterine carcinoma in the stop-exposure group was significantly greater than that in the vehicle-control group; a slight increase in the incidence of squamous cell carcinoma of the uterus occurred in the group at 220 µg/kg bw, and single incidences occurred at 460 µg/kg bw, 1000 µg/kg bw, and in the stop-exposure group. There were slightly increased incidences of exocrine pancreatic adenoma in core-study groups receiving PCB-118 at doses of 460 µg/kg bw or higher.

Table 3.3 Description of binary mixtures of PCB-126 and PCB-153 given to rats in a study of carcinogenicity by the NTP (2006c)

Group	Total TEQ (ng TEQ/kg bw)	Mass	
		PCB-126 (ng/kg bw)	PCB-153 (µg/kg bw)
<i>Constant ratio mixture</i>			
1	Vehicle control	0	0
2	1	10	10
3	10	100	100
5	30	300	300
7	100	1000	1000
<i>Varying ratio mixture</i>			
1	Vehicle control	0	0
4	30	300	100
5	30	300	300
6	30	300	1000

PCB, polychlorinated biphenyl; TEQ, toxic equivalent

(d) PCB-126 and PCB-153

Rat

The NTP conducted a 2-year study that was designed to assess the carcinogenicity of a mixture of PCB-126 and PCB-153 in a constant ratio, and a mixture of PCB-126 and PCB-153 in varying ratios to assess the effect of increasing PCB-153 (NTP, 2006c; Yoshizawa *et al.*, 2009). Groups of 81 or 80 female Harlan Sprague-Dawley rats (age, 8 weeks) received a mixture of PCB-126 and PCB-153 in corn oil : acetone (99 : 1) by gavage, 5 days per week, for up to 105 weeks. Dose groups were referred to by the total concentrations of toxic equivalents (TEQ) provided by the PCBs in the mixture per kg bw in each group (see Table 3.3); a control group of 81 female rats received the corn oil : acetone vehicle only (group 1). Ten rats per group were evaluated at 14, 31, and 53 weeks. At 2 years, the incidences of hepatocellular adenoma (single or multiple) in group 7 (constant ratio; TEQ, 100 ng/kg bw), and of cholangiocarcinoma (single or multiple) in group 5 (constant ratio; TEQ, 30 ng/kg bw) or group 7 were significantly increased. The incidence of hepatocholangioma was also significantly increased in group 7. Two

rats in group 7 had hepatocellular carcinoma; no hepatocellular carcinoma was reported in the historical vehicle controls. In the varying-ratio study, increasing the proportion of PCB-153 significantly increased the incidences of hepatocellular adenoma and cholangiocarcinoma. In the constant-ratio study, the incidence of cystic keratinizing epithelioma of the lung was significantly increased in group 7. In addition, one squamous cell carcinoma was reported in group 5 and one in group 7. Significantly increased incidences of gingival squamous cell carcinoma of the oral mucosa occurred in groups 5 and 7. There was also a slight increase in the incidence of uterine squamous cell carcinoma in group 5.

(e) PCB-118 and PCB-126

Rat

Groups of 81 female Harlan Sprague-Dawley rats (age, 9 weeks) were given a binary mixture of PCB-118 and PCB-126 (see Table 3.4) at a dose of 0 (vehicle control), 7, 22, 72, 216 ng TEQ/kg bw, by gavage in corn oil : acetone (99 : 1), 5 days per week, for up to 104 weeks; a group of 86 female rats received the mixture at a dose of 360 ng TEQ/kg bw (Yoshizawa *et al.*, 2005, 2007,

Table 3.4 Composition of a mixture of PCB-118 and PCB-126 given to rats in a study of carcinogenicity by the NTP (2006d)

	PCB-118	PCB-126	PCB-77 ^a	PCB-167 ^a
Percentage of bulk mass ^b	98.5	0.6	0.2	0.5
Percentage of total TEQ ^c	13.7	86.3	0.03	0.007

^a Present as contaminants that were not considered to contribute to the dioxin-like activity of the bulk synthesized test article

^b Based on the level of each compound present in the bulk synthesized test article

^c Assuming WHO toxic equivalency factor (TEF) values of 0.1 (PCB-126), 0.0001 (PCB-118), 0.0001 (PCB-77) and 0.00001 (PCB-167)
PCB, polychlorinated biphenyl; TEQ, toxic equivalent

2009; NTP, 2006d). Ten rats per group were evaluated at 14, 31, or 53 weeks. In the stop-exposure group, 50 female rats received the mixture at a dose of 360 ng TEQ/kg bw for 30 weeks, and then the vehicle only for the remainder of the study. The dose groups are described in Table 3.5. The mixture contained predominantly PCB-118 (by mass) and PCB-126 (by TEQ), but also contained PCB-77 and PCB-167 as contaminants that were not considered to contribute to the dioxin-like activity of the bulk synthesized material (see Table 3.4).

No rats at 216 or 360 ng TEQ/kg bw survived to the end of the study; survival in the stop-exposure group was also significantly lower than in the vehicle-control group, with only 10 rats surviving to the end of the study. Mean body weights of rats receiving 72 ng TEQ/kg bw or more were lower than those of rats in the vehicle-control group throughout most of the study. At 2 years, the incidences of cholangiocarcinoma (single or multiple, combined) and cholangiocarcinoma (multiple) were significantly increased in groups receiving 72 ng TEQ/kg bw or more. The incidence of hepatocellular adenoma was also significantly increased in the groups at 216 and 360 ng TEQ/kg bw. In addition, single occurrences of hepatocholangioma, cholangioma, or hepatocellular carcinoma were observed in some groups receiving 72 ng TEQ/kg bw or more. At 53 weeks, the incidence of cystic keratinizing epithelioma of the lung was significantly increased in the group at 216 ng TEQ/kg bw. At 2 years, significantly increased incidences of cystic keratinizing

epithelioma (single or multiple, combined) and of cystic keratinizing epithelioma (multiple) were reported in groups receiving 72 ng TEQ/kg bw or more. Non-statistically significant increased incidences of gingival squamous cell carcinoma of the oral mucosa were observed at the end of the 2-year study.

3.1.2 Commercial mixtures of PCBs

(a) Aroclor 1254

(i) Mouse

In a study on the activity of Aroclor 1254 in mice with different aryl hydrocarbon receptor (AhR) phenotypes, groups of 23–34 male C57BL/6, DBA/2, or B6D2F1 mice (age, 5 weeks) were initiated with a single intraperitoneal dose of *N*-nitrosodiethylamine (NDEA) at 0 or 90 mg/kg bw, in tricapylin. Three weeks later, the mice were placed on a diet containing Aroclor 1254 at a concentration of 100 ppm or the control diet for 20 weeks. After the promotion phase, the mice were left untreated until the terminal kill at age 52 weeks. Aroclor 1254 alone did not increase the incidence of tumours of the lung or liver in any of the three strains compared with their respective controls (Beebe *et al.*, 1995).

Four groups of 50 male BALB/cJ inbred mice (age, 5–6 weeks) were fed diets containing Aroclor 1254 (mixed with corn starch) at a concentration of 0 (control) or 300 ppm for up to 11 months (Kimbrough & Linder, 1974; Faroon *et al.*, 2001). After 6 months of exposure, one group of treated mice was fed the standard diet,

Table 3.5 Doses of PCB-118 and PCB-126 given to rats in a study of carcinogenicity by the [NTP \(2006d\)](#)

Dose (ng TEQ/ kg bw)	Contribution to dose by mass ^b				Contribution to dose by TEQ ^c (ng TEQ/kg bw)				Total nominal dose by TEQ ^c (ng TEQ/kg bw)
	PCB-118 (µg/kg bw)	PCB-126 (ng/kg bw)	PCB-77 ^a (ng/kg bw)	PCB-167 ^a (ng/kg bw)	PCB- 118	PCB- 126	PCB- 77 ^a	PCB- 167 ^a	
7	10 ^d	62	20	50	1.0	6.2	0.002	0.0005	7.2
22	30 ^d	187	60	150	3.0	18.7	0.006	0.0015	21.6
72	100 ^d	622	200	500	9.9	62.2	0.02	0.005	72.1
216	300 ^d	1866	600	1500	29.6	186.6	0.06	0.015	216.2
360	500 ^d	3110	1000	2500	49.3	311.0	0.1	0.025	360.4

^a Present as contaminants that were not considered to contribute to the dioxin-like activity of the bulk synthesized test article

^b Based on the level of each compound present in the bulk synthesized test article

^c Assuming WHO TEF (toxic equivalency factor) values of 0.1 (PCB-126), 0.0001 (PCB-118), 0.0001 (PCB-77) and 0.00001 (PCB-167). TEQ value for PCB-118 was calculated assuming 98.5% of bulk material is PCB-118

^d Nominal dose (µg/kg bw) of bulk synthesized material
PCB, polychlorinated biphenyl; TEQ, toxic equivalent

while the other treated group was fed the experimental diet for an additional 5 months; the two control groups were fed plain chow for an additional 5 months. Only one of 24 surviving mice given Aroclor 1254 for 6 months had a hepatoma [histopathology not further specified], while the incidence of hepatoma in the 22 surviving mice fed Aroclor 1254 for 11 months was significantly increased (10 out of 22; $P < 0.001$). Hepatomas were not found in any of the mice in the control groups.

(ii) Rat

Groups of 24 male and 24 female F344 rats (age, 7 weeks) were fed diets containing Aroclor 1254 at a concentration of 0, 25, 50, or 100 ppm in corn oil for up to 105 weeks ([NTP, 1978](#); [Ward, 1985](#); [Safe, 1989](#); [Silberhorn et al., 1990](#); [Faroon et al., 2001](#)). In males, hepatocellular adenoma was observed in one, two, and five of the rats at the lowest, intermediate, and highest dose, respectively, and hepatocellular carcinoma was observed in two rats at the highest dose; the incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) in males at the highest dose were statistically significantly increased. Hepatocellular tumours were

not observed in controls. Non-statistically significant low incidences of rare adenocarcinomas of the glandular stomach were observed in both sexes. Adenocarcinoma of the glandular stomach was not observed in controls. The historical incidence of adenocarcinoma of the glandular stomach at the study laboratory (6 out of 600 males [1%], 2 out of 600 females [0.3%]) suggested that the occurrence of these tumours, although not statistically significant, may have been related to the administration of Aroclor 1254. There was a statistically significant dose-related trend in the combined incidences of lymphoma and leukaemia in male rats, but incidence in each dose group was not statistically significantly different from that in matched controls. [Morgan et al. \(1981\)](#) and [Ward \(1985\)](#) re-examined the gastrointestinal lesions observed in the study by the [NTP \(1978\)](#) and found a dose-related increase in the incidence of metaplasia of the glandular stomach, and also found adenocarcinoma of the glandular stomach in six treated rats. When compared with the incidence of adenocarcinoma of the glandular stomach in historical controls (1 out of 3548), the total incidence (6 out of 144 male and female rats treated with Aroclor 1254) was statistically significant.

*(b) Aroclor 1260**Rat*

Groups of 200 female Sherman rats (age, 21–26 days) were fed diets containing Aroclor 1260 at a concentration of 0 (control) or 100 ppm for approximately 21 months ([Kimbrough et al., 1975](#)). The rats were killed at age 23 months. There were statistically significant increases in the incidences of “hepatic neoplastic nodules” and of hepatocellular carcinoma in rats receiving Aroclor 1260 compared with controls. The hepatocellular tumours were re-evaluated histologically by a panel of pathologists using contemporary diagnostic criteria and nomenclature ([Moore et al., 1994](#)). Lesions that had been previously diagnosed as “neoplastic nodules” were reclassified as either hepatocellular hyperplasia or hepatocellular adenoma. In general, the results of the re-evaluation were consistent with those of the original evaluation.

Groups of 32 male Wistar rats (age, 5 weeks) were fed a 10% protein diet containing Aroclor 1260 (dissolved in coconut oil) at a concentration of 0 (control), 50, or 100 ppm for 120 days ([Rao & Banerji, 1988](#); [Silberhorn et al., 1990](#)). Controls were fed diet mixed with coconut oil. The incidences of “liver neoplastic nodules” [liver tumours] were significantly increased in both groups of treated rats; however, the incidence of tumours in rats fed the higher dose was lower than that in rats fed the lower dose.

Groups of 70 male and 70 female Sprague-Dawley rats were fed a diet containing Aroclor 1260 at a concentration of 100 ppm for 16 months, followed by diet containing Aroclor 1260 at 50 ppm for an additional 8 months, and then basal diet for 5 months ([Norback & Weltman, 1985](#); [Safe, 1989](#); [Silberhorn et al., 1990](#); [Moore et al., 1994](#); [Faroon et al., 2001](#)). Groups of 63 males and 63 females served as controls and received the basal diet supplemented with corn oil for 18 months, and then the basal diet only for the remainder of the study. The medial

and left lobes of the liver of 10 rats (two male controls, two female controls, three PCB-treated males and three PCB-treated females, for each time-point) were removed at 1, 3, 6, 9, 12, 15, and 18 months. In treated rats that survived 18 months or longer, malignant hepatic tumours (adenocarcinoma and/or trabecular carcinoma) were found in 43 out of 47 females, but only in 2 out of 46 males. The individual incidences of adenocarcinoma and of trabecular carcinoma in PCB-treated females were significantly greater than in controls. Hepatic neoplastic nodules [benign hepatocellular tumours] occurred in 5 out of 46 males, and 2 out of 47 females. A single hepatic neoplastic nodule occurred in a female control rat. PCB-exposed rats developed cystic cholangioma in 2 out of 46 males, and 5 out of 47 females [non-significant], versus 0 out of 32 males and 1 out of 49 females among the controls. Preneoplastic lesions of the biliary tract, referred to as simple and cystic cholangioma, also occurred at a higher incidence in treated males and females (30% and 45%, respectively).

*(c) Aroclor 1016, 1242, 1254, and 1260**Rat*

A comprehensive comparative long-term study of toxicity and carcinogenicity was conducted with four of the most widely used commercial Aroclor mixtures: Aroclor 1016, 1242, 1254, and 1260 ([Mayes et al., 1998](#); [Faroon et al., 2001](#); [Brown et al., 2007](#)). Groups of 50 male and 50 female Sprague-Dawley rats (age, 6–8 weeks) were fed diets containing Aroclor 1016, 1242, 1254, or 1260 at doses ranging from 25 to 200 ppm (three dose levels for Aroclor 1016, 1254 and 1260, and two dose levels for Aroclor 1242) for 24 months. Groups of 100 males and 100 females served as controls. Aroclor 1016, 1242, 1254, and 1260 contained polychlorinated dibenzodioxins (PCDDs) at concentrations of 0.6, 0, 20, and 0 ppb, respectively, and polychlorinated dibenzofurans (PCDFs) at concentrations

of 0.035, 2.9, 23, and 4.9 ppm, respectively. The basal diet contained PCBs at less than 0.15 ppm (estimated dose, < 0.01 mg/kg bw per day). Aroclor 1254 was treated to remove > 99% of the PCDFs. Feeding with diets containing Aroclor led to increased incidences of hepatic neoplasms (primarily hepatocellular adenoma) that were highly sex-dependent (females > males) and that differed between Aroclor mixtures. For females, the incidences of hepatocellular adenoma and of hepatocellular carcinoma increased with dose, with the following pattern: Aroclor 1254 > Aroclor 1260 > Aroclor 1242 > Aroclor 1016. The number of females bearing multiple hepatocellular tumours also increased in a dose-related manner for all Aroclor mixtures, and the highest numbers were in the groups receiving the intermediate and highest dose of Aroclor 1254, and the highest dose of Aroclor 1260. In addition, in females receiving Aroclor 1260, there was an increase in the incidence of cholangioma. In males, an increased incidence of hepatocellular adenoma was observed only in the group receiving Aroclor 1260 at the highest dose. The incidence of follicular cell adenoma of the thyroid gland was significantly increased in males in a non-dose-dependent manner; these increases were induced by Aroclor 1242 (both doses), Aroclor 1254 (all doses), and Aroclor 1260 (lowest and intermediate doses).

(d) *Kanechlor 300, 400, and 500*

(i) *Mouse*

Groups of 20 male and 20 female dd strain albino mice [age not reported] were given diets containing one of three PCB mixtures (Kanechlor 300, 400, or 500) at a concentration of 0, 100, 250, or 500 ppm for 24 or 32 weeks ([Nagasaki et al., 1975](#)). The incidence of hepatocellular carcinoma was significantly increased in male and female mice given Kanechlor 500 at 500 ppm for 32 weeks. No tumours of the liver were found in mice fed Kanechlor 500 at dietary

concentrations of 100 or 250 ppm, or the lesser chlorinated commercial mixtures Kanechlor 400 or Kanechlor 300 at any of the three dietary concentrations at 24 or 32 weeks.

Groups of 12 male dd strain albino mice (age, 8 weeks) were fed basal diets supplemented with one of three PCB mixtures (Kanechlor 300, 400, or 500) at a concentration of 100, 250, or 500 ppm for 32 weeks; a control group of six mice was fed basal diet alone ([Ito et al., 1973](#); [Silberhorn et al., 1990](#); [Faroon et al., 2001](#)). The incidences of hepatocellular carcinoma (5 out of 12 [not significant]) and liver hyperplastic nodules [some of which may have been hepatocellular adenomas] (7 out of 12 [$P < 0.05$]) were increased in mice fed diets containing Kanechlor 500 at 500 ppm compared with controls (0 out of 6). Hepatic lesions were not found in mice fed Kanechlor 500 at lower doses, or in mice exposed to the less chlorinated mixtures Kanechlor 400 or Kanechlor 300 for 32 weeks. Other histopathological changes in mice treated with PCBs included oval-cell proliferation, bile duct proliferation, hepatocyte hypertrophy, and amyloidosis. [The Working Group noted that the study may have been limited by the small number of mice, the relatively short treatment period, and the absence of an observation period after treatment.]

(ii) *Rat*

A group of 10 male and 10 female Donryu rats (age, 10 weeks) were fed diet containing Kanechlor 400 at a concentration of 38.5 ppm for 4 weeks, then the initial concentration was increased (based on body weights) twice for 8 weeks, 4 times for 3 weeks, 8 times for 3 weeks, and 16 times for 8 weeks ([Kimura & Baba, 1973](#); [Silberhorn et al., 1990](#)). The latter concentration was decreased to 12 times for 32 weeks because body weights were decreasing markedly. Rats were then fed basal diet until moribund, up to 560 days. A group of five males and five females fed basal diets served as controls. Treatment with Kanechlor 400 (duration, 400 days) caused

a significant increase in the incidence of multiple adenomatous nodules [hepatocellular adenoma] in females. None of the treated males developed adenomatous nodules. [The Working Group noted that the study may have been limited by the small numbers of animals, and may have exceeded the maximum tolerated dose.]

(e) *Clophen A 30 and Clophen A 60*

Rat

Male weanling Wistar rats were fed a diet supplemented with Clophen A 30 (42% chlorine by weight) or Clophen A 60 (60% chlorine by weight) at a concentration of 100 ppm, or an estimated dose of 5 mg/kg bw per day, for up to 832 days; controls were fed the basal diet (Schaeffer *et al.*, 1984; Young, 1985; Safe, 1989). Tumour incidence was investigated at intervals of 100 days. After 800 days, the overall incidence of hepatocellular neoplastic nodules, irrespective of time period, was significantly increased in rats fed Clophen A 30 (38 out of 130) or Clophen A 60 (63 out of 126) compared with controls (5 out of 131). The incidence of hepatocellular carcinoma was significantly increased in rats fed Clophen A 60 (61 out of 126 compared with 1 out of 131 controls). The incidences of hepatocellular lesions were re-evaluated by a panel of pathologists using contemporary diagnostic criteria and nomenclature (Moore *et al.*, 1994). Lesions that had been previously diagnosed as neoplastic nodules were now classified as either hepatocellular hyperplasia or hepatocellular adenoma. The results of the re-evaluation were generally consistent with those of the original evaluation.

3.2 Transplacental and perinatal exposure

This section covers those studies for which exposure to PCBs occurred either transplacentally and/or perinatally. This period generally covers exposure from day 1 of gestation until

weaning on postnatal day 21, although it should be noted that weaning can occur at up to age 28 days.

3.2.1 Individual PCBs and binary mixtures

(a) *PCB-126*

See [Table 3.6](#)

Rat

Five groups of pregnant Sprague-Dawley rats were given PCB-126 at a dose of 0 (corn oil), 0.025, 2.5, 250, or 7500 ng/kg bw by gavage on days 13 to 19 of gestation. Female pups from the exposed dams were weaned on postnatal day 21, and subsequently exposed at age 50 days to 7,12-dimethylbenz[*a*]anthracene (DMBA) at a dose of 20 mg/kg bw in corn oil by gavage, and followed until age 170 days (Muto *et al.*, 2001). There was no specific perinatal oral exposure to PCB-126. There was a significant reduction in body weight in the groups of pups at 250 ng/kg bw and 7500 ng/kg bw at postnatal day 21, and at 7500 ng/kg bw at age 30 days. There was a significant reduction in the incidence of DMBA-induced tumours of the mammary gland in the group at 7500 ng/kg bw. In the group at 7500 ng/kg bw, 41% of tumours were adenomas, while tumours in all other groups were mainly adenocarcinomas. [The study design was not a full carcinogenesis bioassay of PCBs.]

In a similar study by Wakui *et al.* (2005), four groups of pregnant Sprague-Dawley rats were given PCB-126 at a dose of 0 (corn oil vehicle), 2.5, 250, or 7500 ng/kg bw by gavage on days 13 to 19 of gestation. Female pups from the exposed dams were weaned at postnatal day 21, and subsequently exposed at age 50 days to DMBA at a dose of 100 mg/kg bw in corn oil by gavage, and followed until age 150 days. As in the study by Muto *et al.* (2001), there was a significant reduction in the incidence of adenocarcinoma of the mammary gland in the group at 7500 ng/kg bw. [The study design was not a full carcinogenesis bioassay of PCBs.]

Table 3.6 Studies of carcinogenicity in rats exposed perinatally or transplacentally to PCB-126

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
Sprague- Dawley (Japan SLC) (F) 170 day Muto et al. (2001)	Dams were treated with PCB-126 at 0 (corn oil vehicle), 0.025, 2.5, 250, or 7500 ng/kg bw (0.5 mL/rat) by gavage on days 13–19 of gestation. Pups were weaned at PND 21 Female pups (age 50 days) received DMBA at 20 mg/kg bw in corn oil by gavage and observed until age 170 days, or until tumours reached 20 mm in size Group 1: corn oil vehicle Group 2: 0.025 ng/kg bw Group 3: 2.5 ng/kg bw Group 4: 250 ng/kg bw Group 5: 7500 ng/kg bw 45/group	Tumours of the mammary gland: Group 1: 42/45, 3.12 ± 0.74 Group 2: 44/45, 2.77 ± 1.89 Group 3: 42/45, 3.98 ± 2.82 Group 4: 43/45, 5.09 ± 2.42 Group 5: 35/45*, 2.25 ± 1.55	* $P < 0.05$, χ^2 test (decrease)	Not a full carcinogenesis bioassay In the group at 7500 ng/kg bw, 41% of tumours were adenomas, whereas in all other groups the tumours were mainly adenocarcinomas
Sprague- Dawley (Japan SLC) (F) 150 day Wakui et al. (2005)	Dams were treated with PCB-126 at 0 (corn oil vehicle), 2.5, 250, 7500 ng/kg bw (0.5 mL/rat) by gavage on days 13–19 of gestation. Pups were weaned at PND 21 Females (age 50 days) received DMBA at 100 mg/kg bw in corn oil by gavage, and were observed until age 150 days Group 1: corn oil vehicle Group 2: 2.5 ng/kg bw Group 3: 250 ng/kg bw Group 4: 7500 ng/kg bw 25/group	Mammary gland, adenocarcinoma: Group 1: 22/25 (88%) Group 2: 21/25 (84%) Group 3: 23/25 (92%) Group 4: 16/25 (64%)*	* $P < 0.05$, χ^2 test (decrease)	Not a full carcinogenicity bioassay

DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; M, male; NDMA, *N*-nitrosodimethylamine; PND, postnatal day; wk, week

(b) PCB-153 and PCB-138

See [Table 3.7](#)*Mouse*

Eight groups of male Swiss Cr:NIH(s) mice were given an intraperitoneal injection of *N*-nitrosodimethylamine (NDMA) at 0 (saline vehicle) or 5 mg/kg bw on postnatal day 4. On postnatal day 8, the mice were treated by gavage with PCB-153 or PCB-138, or a mixture of the two PCBs, each at a single dose of 20 mg/kg bw, or with the vehicle, olive oil ([Anderson et al., 1991](#)). The concentration selected, 20 mg/kg bw, is approximately equivalent to the concentration of each PCB congener in a dose of 500 mg/kg bw of Aroclor 1254. The mice were killed at age 16 weeks. There was no effect of either PCB congener alone or in combination on the incidence of bronchioloalveolar adenoma in the absence of treatment with NDMA. In NDMA-initiated mice, there was a significant increase in the multiplicity of bronchioloalveolar adenoma in mice also exposed to PCB-138. There was no effect of PCB-153, or of PCB-153 plus PCB-138, when compared with controls treated with NDMA only. [This study was not a full carcinogenesis bioassay. It was limited regarding the effect of the PCBs alone without initiation, due to the short duration of observation.]

3.2.2 Commercial mixtures of PCBs

(a) Aroclor 1254

See [Table 3.8](#)*Mouse*

Pregnant CD-1 mice were given a single intraperitoneal injection of Aroclor 1254 at a dose of 0 (corn oil) or 500 mg/kg bw on day 19 of gestation ([Anderson et al., 1983](#)). Suckling mice were given NDMA at 0 (saline vehicle) or 5 mg/kg bw by intraperitoneal injection on postnatal day 4 or 14, or every 3 days on postnatal days 1–22. Mice were weaned at age 4 weeks and examined

at approximately 28 weeks and 18 months. No tumours of the liver were found at 28 weeks in male or female mice exposed in utero to the vehicle or Aroclor 1254 alone without exposure to NDMA. At 18 months, there was no increase in the incidence of tumours of the liver in mice treated with Aroclor 1254 without NDMA exposure. In the groups that were exposed to NDMA on postnatal day 4 or 14, there was no effect of maternal exposure to Aroclor 1254 on the incidence or multiplicity of tumours of the liver in male or female mice. Nevertheless, at 18 months, there was a significant increase in the incidence of “coalescing” tumours of the liver in females exposed on postnatal day 4 and in males exposed on postnatal day 14. There was no effect of maternal exposure to Aroclor 1254 on the incidence or multiplicity of tumours of the liver in male or female pups treated with NDMA between postnatal days 1 and 22. [This study design was not a full carcinogenesis bioassay of PCBs. Although mice were exposed to PCBs before being exposed to NDMA, NDMA acts as an initiator. Thus results from the groups exposed to NDMA plus PCBs are more likely to reflect an effect of the exposure to PCBs in utero on NDMA carcinogenesis.]

Groups of male neonatal Swiss Cr:NIH(s) mice were injected intraperitoneally with NDMA at a dose of 5 mg/kg bw in saline on postnatal day 4 ([Anderson et al., 1986](#)). On postnatal day 8, mice were exposed to Aroclor 1254 at a dose of 0 (control), 50, 250, or 500 mg/kg bw in olive oil by gavage, for 16 or 28 weeks. The study also included two non-initiated groups exposed to Aroclor 1254 at a dose of 0 or 500 mg/kg bw. A significant increase in the average number of bronchioloalveolar adenomas was observed in mice exposed to both NDMA and Aroclor 1254 compared with mice exposed to NDMA only, but not in mice exposed to Aroclor 1254 without NDMA initiation compared with mice exposed to vehicle only.

Table 3.7 Study of carcinogenicity in mice exposed perinatally to PCB-153 and PCB-138

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
Swiss Cr:NIH(s) (M) 16 wk Anderson <i>et al.</i> (1991)	Intraperitoneal injection on PND 4 with NDMA at 5 mg/kg bw or saline vehicle Exposure on PND 8 to PCBs (in olive oil) at 20 mg/kg bw by gavage until age 16 wk Group 1: NDMA Group 5: NDMA + PCB-153 Group 6: NDMA + PCB-138 Group 7: NDMA + PCB-153 + PCB-138 Group 8: saline/olive oil Group 2: PCB-153 Group 3: PCB-138 Group 4: PCB-153 + PCB-138 Number/group, NR	Bronchioloalveolar adenoma: Group 1: 15/55 (27%), 0.42 ± 0.11 Group 5: 13/53 (24%), 0.3 ± 0.08 Group 6: 21/50 (42%), 1.0 ± 0.3* Group 7: 14/46 (30%), 0.52 ± 0.13 Group 8: 0/26 Group 2: 0/32 Group 3: 0/31 Group 4: 0/34	* <i>P</i> = 0.014 vs group 1	Purity, NR Not a full carcinogenicity bioassay Concentration of PCBs (20 mg/kg bw) is approximately equivalent to that of each PCB congener in Aroclor 1254 at 500 mg/kg bw

M, male; NDMA, *N*-nitrosodimethylamine; PCB, polychlorinated biphenyl; PND, postnatal day; vs, versus

Table 3.8 Studies of carcinogenicity in mice exposed perinatally or transplacentally to Aroclor 1254

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
CD-1 (M, F) 28 wk and 18 mo Anderson et al. (1983)	Pregnant dams given a single intraperitoneal injection of Aroclor 1254 at 0 (olive oil vehicle) or 500 mg/kg bw on day 19 of gestation. Progeny then injected intraperitoneally with saline (experiment 1) or NDMA at 5 mg/kg bw on PND 4 (experiment 2), PND 14 (experiment 3), or every 3 days from PND 1 to 22 (experiment 4) Group 1: olive oil (F, 28 wk) Group 2: Aroclor 1254 (F, 28 wk) Group 3: olive oil (F, 18 mo) Group 4: Aroclor 1254 (F, 18 mo) Group 5: olive oil (M, 28 wk) Group 6: Aroclor 1254 (M, 28 wk) Group 7: olive oil (M, 18 mo) Group 8: Aroclor 1254 (M, 18 mo) Number of mice/group, NR	<i>Experiment 1 (no NDMA):</i> Liver tumours: 0/23, 0/21, 1/31, 1/23, 0/21, 0/23, 12/23, 8/25 <i>Experiment 2 (NDMA on PND 4):</i> Liver tumours: 3/17, 3/21, 21/29, 17/20, 17/23, 14/24, 27/28, 17/17 Liver (coalescing) tumours: 0/17, 0/21, 7/29, 13/20*, 17/23, 14/24, 27/28, 17/17 <i>Experiment 3 (NDMA on PND 14):</i> Liver tumours: 2/18, 0/19, 16/24, 9/19, 9/26, 1/19**, 18/19, 18/19 Liver (coalescing) tumours: 0/18, 0/19, 3/24, 1/19, 0/26, 0/19, 8/19, 14/19***	NS NS * $P < 0.01$ (Fisher exact test) ** $P < 0.04$ (Fisher exact test), decrease *** $P < 0.035$ (Fisher exact test)	Purity, NR Tumour incidence and multiplicity in progeny (from dams treated with Aroclor 1254) exposed to NDMA every 3 days from PND 1 to PND 22 (experiment 4) were not increased and are not shown
Swiss Cr:NIH(s) (M) 16 or 28 wk Anderson et al. (1986)	Intraperitoneal injection of NDMA (0 or 5 mg/kg bw) in saline on PND 4 followed on PND 8 by exposure to Aroclor 1254 in olive oil by gavage Groups were exposed for 16 or 28 wk to: NDMA + Aroclor 1254 (50 mg/kg bw); NDMA + Aroclor 1254 (250 mg/kg bw); NDMA + Aroclor 1254 (500 mg/kg bw); NDMA + olive oil; saline + Aroclor 1254 (500 mg/kg bw); saline + olive oil Number/group, NR	Bronchioloalveolar adenoma (average no. of tumours/no. of examined animals): 16 wk: 5.7/16, 5.1/12, 11.8/14*, 6.1/17, 0/13, 0.2/6 28 wk: 7.9/15, 8.6/14, 11.9/16**, 6.6/16, 0.2/19, 0.1/7	* $P < 0.05$ ** $P < 0.01$	Purity, NR Not a full carcinogenicity bioassay. Short duration

Table 3.8 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
Swiss Cr:NIH(s) (M) up to 72 wk Anderson et al. (1994)	Intraperitoneal injection on PND 4 with NDMA at 5 mg/kg bw or saline vehicle. At age 8 days, mice received Aroclor 1254 at 250 mg/kg bw by gavage in olive oil or vehicle only. Mice were killed when moribund or at age 16, 28, 52, or 72 wk Groups were exposed to: NDMA; NDMA + Aroclor 1254; Aroclor 1254; saline/oil Number/group, NR	<i>Bronchioloalveolar adenoma:</i> Age 28 wk: 7/23 ^a (30%), 0.5 ± 1.1 ^b ; 19/27 ^a (70%), 1.9 ± 2.9 ^b ; 0/13; 0/16 Age 52 wk: 12/25 (48%), 0.6 ± 0.8 ^c ; 15/23 (65%), 2.7 ± 3.8 ^c ; 4/24 (17%), 0.17 ± 0.38; 6/27 (22%), 0.26 ± 0.4 Age 72 wk: 21/23 (91%), 5.1 ± 4.5; 17/23 (74%), 3.9 ± 4.3; 17/25 (68%), 0.9 ± 0.8; 17/39 (44%), 0.6 ± 0.7 <i>Liver adenoma:</i> Age 52 wk: 1/25 ^d (4%), 0.04 ± 0.2; 9/23 ^d (39%), 0.6 ± 0.8; 0/24; 0/27 Age 72 wk: 16/23 (70%), 1.8 ± 2.2; 14/25 (56%), 1.5 ± 2.0; 0/25; 0/39	Matched letters are significantly different from each other ^a P = 0.01 ^b P = 0.0033 ^c P = 0.0496 ^d P = 0.0004	Purity, NR Not a full carcinogenicity bioassay

mo, month; NDMA, N-nitrosodimethylamine; NR, not reported; NS, not significant; PND, postnatal day; wk, week

In a subsequent experiment, groups of neonatal male Swiss Cr:NIH(s) mice were given an intraperitoneal injection of NDMA at a dose of 0 (saline vehicle) or 5 mg/kg bw on postnatal day 4, then given Aroclor 1254 at a dose of 0 or 250 mg/kg bw in olive oil on day 8 by gavage, and killed at age 16, 28, 52, or 72 weeks ([Anderson et al., 1994](#)). At age 28 weeks, the incidence of bronchioloalveolar adenoma in mice initiated with NDMA was increased 2.5-fold by treatment with Aroclor 1254. The multiplicity of bronchioloalveolar adenoma was enhanced fourfold by treatment with Aroclor 1254 for 28 or 52 weeks. By 72 weeks, tumour numbers, although high, were similar in the groups receiving NDMA only, and NDMA plus Aroclor 1254. There was an increased incidence of liver adenoma at 52 weeks in mice receiving NDMA plus Aroclor 1254 compared with mice receiving NDMA only. By 72 weeks, the incidences in the groups receiving NDMA or NDMA plus Aroclor 1254 were similar. [This study was not a full carcinogenesis bioassay of PCBs.]

(b) *Kanechlor 500*

See [Table 3.9](#)

Rat

Pregnant Wistar rats were exposed to Kanechlor 500 at a dose of 0 (olive oil vehicle), 40, or 200 mg/kg bw by gavage on days 5, 10, and 15 of gestation ([Nishizumi, 1980](#)). Male and female pups were subsequently weaned and given drinking-water containing NDEA at 50 ppm for 5 weeks to induce liver tumours [mainly hepatocellular carcinomas] that were evaluated after 20 and 24 weeks. The average concentration of total PCBs in the liver at 4 weeks was 1 ppm, 18 ppm and 360 ppm in the groups at 0 (vehicle), 40 mg/kg bw and 200 mg/kg bw, respectively, indicating clear transfer from the dam to the offspring. In both males and females, there was a decrease in the multiplicity of NDEA-initiated tumours of the liver. [This study was not a full carcinogenesis bioassay.]

3.2.3 Mixtures of PCBs and other chlorinated agents found in human milk fat

(a) *Mixture of non-ortho PCBs, PCDFs, and PCDDs*

See [Table 3.10](#)

Rat

Female Sprague-Dawley rats were exposed by gavage at age 1, 5, 10, 15, and 20 days to a mixture of three non-ortho PCBs [PCB-77, PCB-126, and PCB-169], six PCDDs, and seven PCDFs, or were exposed to the vehicle (corn oil) only ([Desaulniers et al., 2004](#)). The concentrations of these agents in the mixture were based on the concentrations of dioxin-like congeners found in human milk fat, and the doses administered were equal to 10 times, 100 times, or 1000 times the quantities found in milk fat. At age 50 days, groups of rats were injected intraperitoneally with *N*-methyl-*N*-nitrosourea (MNU) at a dose of 0 or 30 mg/kg bw to induce the development of tumours of the mammary gland. At age 32 weeks, in those groups not treated with MNU, there was a significant increase in the incidence of benign lesions of the mammary gland (adenoma, fibroadenoma, and hyperplasia) after exposure to the 1000-times mixture. In the MNU-treated groups, there was no effect of exposure to the mixture on the incidences of benign lesions or malignant tumours of the mammary gland. [This study was not a full carcinogenesis bioassay. Given the presence of PCDDs and PCDFs in the mixture, conclusions regarding the effect of PCBs alone could not be drawn from this study.]

(b) *Mixture of PCBs, DDT, and DDE*

See [Table 3.11](#)

Rat

Neonatal female Sprague Dawley rats were exposed to a mixture of 19 PCB-congeners, *p,p'*-dichlorodiphenyltrichloroethane (DDT), and *p,p'*-dichlorodiphenyldichloroethene (DDE)

Table 3.9 Study of carcinogenicity in rats exposed transplacentally and perinatally to Kanechlor 500

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
Wistar (M, F) up to 29 wk Nishizumi (1980)	Dams were given Kanechlor 500 at 0 (olive oil vehicle), 40, or 200 mg/kg bw by gavage on days 5, 10 and 15 of gestation. Male and female offspring were given drinking-water containing NDEA at 50 ppm for 5 wk, and were evaluated 20 and 24 wk after NDEA exposure Group 1: vehicle (olive oil) Group 2: Kanechlor 500 at 40 mg/kg bw Group 3: Kanechlor 500 at 200 mg/kg bw 6–8 M and 6–8 F/group	Liver tumours (≥ 5 mm) M (20 wk): Group 1: 6/7 (86%), 3.0 \pm 0.7 Group 2: 6/8 (75%), 1.3 \pm 0.4* Group 3: 4/6 (50%), 1.0 \pm 0.4* F (20 wk): Group 1: 5/8 (62.5%), 1.1 \pm 0.4 Group 2: 4/8 (50%), 0.6 \pm 0.3 Group 3: 0/8, 0* M (24 wk): Group 1: 8/8 (100%), 4.6 \pm 0.7 Group 2: 6/6 (100%), 2.8 \pm 0.7 Group 3: 5/7 (71%), 2.0 \pm 0.7* F (24 wk): Group 1: 4/7 (57%), 1.4 \pm 0.5 Group 2: 3/7 (43%), 0.7 \pm 0.4 Group 3: 2/8 (25%), 0.4 \pm 0.3	* $P < 0.05$ (decrease)	Not a full carcinogenesis bioassay Liver tumours were mainly hepatocellular carcinomas, with some neoplastic nodules

F, female; M, male; NDEA, N-nitrosodiethylamine; wk, week

Table 3.10 Studies of carcinogenicity in rats exposed perinatally to a mixture of non-ortho PCBs, PCDDs, and PCDFs

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence of tumours	Significance	Comments
Sprague-Dawley Charles River, St-Constant, QC (F) 32 wk Desaulniers et al. (2004)	Mixture (5 mL/kg bw) in corn oil given to neonates at age 1, 5, 10, 15, and 20 days, by gavage. Mixture contained 0 (vehicle), 1, 10, 100, or 1000 times the amount a human baby would consume. MNU was injected intraperitoneally (30 mg/kg bw in saline) at age 50 days. The rats were killed at age 32 wk Without MNU: vehicle (controls), 1000 × mixture	<i>Mammary gland:</i> Benign lesions (adenoma, fibroadenoma, hyperplasia): 4/37, 11/37* Malignant (carcinoma in situ and adenocarcinoma): 1/37, 4/37	* $P < 0.05$	Purity, NR Short duration; not a full carcinogenicity bioassay The concentrations of each chemical included in the mixture (three non-ortho PCBs [PCB-77, PCB-126, and PCB-169], six PCDDs and seven PCDFs) were based on the concentrations found in human milk fat Description of benign lesions of the mammary gland did not differentiate between non-neoplastic (hyperplasia) and neoplastic (adenoma, fibroadenoma) lesions Mixture included PCDDs and PCDFs, so conclusions could not be made regarding the effect of PCBs alone
	With MNU: vehicle (controls), 1 × mixture, 10 × mixture, 100 × mixture, 1000 × mixture 31–40/group	Benign lesions: 11/35, 8/32, 14/32, 12/31, 10/40 Malignant tumours: 24/35, 18/32, 19/32, 21/31, 25/40	NS	

F, female; M, male; MNU, *N*-methyl-*N*-nitrosourea; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; wk, week

(Desaulniers *et al.*, 2001). The PCB-congeners in the mixture were those detected in more than 75% of samples of breast milk from Canadian women and were included in proportions determined by their median concentrations measured in milk fat. The PCBs were: non-*ortho* (PCB-77, PCB-126, PCB-169), mono-*ortho* (PCB-28, PCB-66, PCB-74, PCB-118, PCB-156), and di-*ortho* (PCB-99, PCB-128, PCB-138, PCB-153, PCB-170, PCB-180, PCB-183, PCB-187, PCB-194, PCB-201, PCB-203) substituted congeners. In this study, five groups of neonatal rats were exposed to the mixture composed of DDT, its major metabolite DDE, and PCBs at 0 (corn oil), 10, 100, or 1000 times their concentrations in breast milk, by gavage, starting at age 1, 5, 10, 15, or 20 days. For comparison purposes, an additional group was exposed by gavage at age 18 days to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) at a concentration of 2.5 µg/kg bw. On day 21, all treatment groups (except for a control group that received corn oil only, and a group that received the 1000-times mixture) received a single intraperitoneal injection of MNU (30 mg/kg bw) in saline. Animals were observed up to 308 days. Seven to nine rats from the groups not exposed to MNU were killed between ages 55 and 62 days; the remaining rats were killed at 224 days. MNU-treated rats were killed when palpable tumours reached 1 cm, or by day 308 if no palpable tumour was detected. Sporadic incidences of lesions of the mammary gland were observed in the groups not treated with MNU (0 and 1000-times mixture). On the contrary, a large number of lesions of the mammary gland (including hyperplasia, the most common lesion observed) were seen in MNU-treated rats, and there was a significant effect of the 1000-times mixture ($P = 0.05$) on the median number of combined benign and malignant lesions of the mammary gland when compared to the MNU-only treated rats. There was no significant effect on the incidence of any specific tumour type, either benign or malignant, or the combined incidence of

benign and malignant neoplasms. [Given that the mixture contained DDT and DDE, in addition to PCBs, the Working Group considered this study as a co-carcinogenicity study, and conclusions regarding the effect of PCBs alone could not be made.]

3.2.7 PCB metabolites: 4'-OH-PCB-30 and 4'-OH-PCB-61

See [Table 3.12](#)

Mouse

Neonatal female BALB/cCrg1 mice were exposed 16 hours after birth onwards to: 20 or 200 µg of 2',4',6'-trichloro-4-biphenylol [4'-OH-PCB-30]; 40 or 400 µg of 2',3',4',5'-tetrachloro-4-biphenylol [4'-OH-PCB-61]; 10 µg of 4'-OH-PCB-30 plus 10 µg of 4'-OH-PCB-61, or 100 µg of 4'-OH-PCB-30 plus 100 µg of 4'-OH-PCB-61 (Martinez *et al.*, 2005). Exposure occurred via daily subcutaneous injections for 5 days and the mice were held for 20 months. [The neonatal mouse model has previously been used as a model for diethylstilbestrol-induced carcinogenesis after exposure in utero. The BALB/c mouse is known to be sensitive to the induction of cervicovaginal tumours by estrogens.] Significant treatment-related increases in the incidence of cervicovaginal tumours were observed for the groups treated with 4'-OH-PCB-30. Modest but statistically significant increases in the incidence of cervicovaginal tumours were also seen in both groups exposed to 4'-OH-PCB-61, and to the combination of 4'-OH-PCB-30 + 4'-OH-PCB-61 at the higher dose. There was also a significant effect of 4'-OH-PCB-61 at the lower dose on the incidence of carcinoma of the mammary gland.

Table 3.12 Study of carcinogenicity in mice exposed perinatally to 2',4',6'-trichloro-4-biphenylol (OH-PCB-30) and/or 2',3',4',5'-tetrachloro-4-biphenylol (4'-OH-PCB-61)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence of tumours	Significance	Comments
BALB/cCrlj (F) Up to 20 mo Martinez et al. (2005)	Daily subcutaneous injections of 20 µL for 5 days starting 16 hours after birth. Mice were weaned at age 21 days. Examination daily for premature vaginal opening for the first 35 days of life and checks monthly to detect concretions. When concretions were found, the mice were removed from the study. All mice that survived to age 20 mo were killed Groups were injected with: sesame oil vehicle (control); 20 µg OH-PCB-30; 200 µg OH-PCB-30; 40 µg OH-PCB-61; 400 µg OH-PCB-61; 10 µg OH-PCB-30 + 10 µg OH-PCB-61; or 100 µg OH-PCB-30 + 100 µg OH-PCB-61 Number/group, NR	Cervicovaginal tract carcinoma: 0/33, 2/33, 10/22**, 4/30*, 5/24*, 3/36, 8/21* Mammary gland carcinoma: 0/33, 5/33, 0/22, 4/30*, 1/24, 3/36, 0/21	* $P < 0.05$ (Fisher exact test) ** $P < 0.01$ (Fisher exact test)	Purity, NR The BALB/c mouse is sensitive to the induction of cervicovaginal tumours by estrogens. The inbred BALB/cCrlj strain has a low incidence of tumours of the mammary gland. The neonatal mouse model has previously been used as a model for diethylstilbestrol-induced carcinogenesis after exposure in utero Carcinomas of the cervicovaginal tract were mainly squamous cell carcinomas and adenosquamous carcinomas

F, female; mo, month; NR, not reported; PCB, polychlorinated biphenyl

3.3 Initiation–promotion and co-carcinogenicity studies

See [Table 3.13](#)

3.3.1 Initiation–promotion studies

(a) PCB-153

A study was carried out to determine whether PCB-153 had promoting activity in NDEA-initiated tumours of the liver in male B6129SF2/J mice, and whether the deletion of the NF- κ B p50 subunit influenced liver carcinogenesis ([Glauert et al., 2008](#)). Four groups of 14–17 wildtype and transgenic mice were injected intraperitoneally with NDEA (90 mg/kg bw in saline) at 9 weeks of age. After a 2-week recovery period, both wildtype and NF- κ B p50^{-/-} mice were injected intraperitoneally with PCB-153 at a dose of 0 (corn oil) or 300 μ mol/kg bw every 14 days for a total of 20 injections. Mice were then maintained for an additional 15 weeks before being killed. Hepatocellular tumours were mainly classified as hepatocellular carcinoma. The incidence of hepatocellular tumours was higher in wildtype mice treated with PCB-153 than in wildtype mice receiving corn oil only. The deletion of p50 decreased the incidence of hepatocellular tumours in mice treated with PCB-153 or corn oil only.

(b) Aroclor 1254

(i) Mouse

In a study to determine whether Aroclor 1254 promoted the induction of liver nodules after initiation with NDEA, groups of male CD-1 mice were first given drinking-water containing NDEA at a dose of 0 or 8 μ g/g bw per day, for 8 weeks ([Gans & Pintauro, 1986](#)). After 2.5 weeks, mice were given Aroclor 1254 as an intraperitoneal dose at 0 (tricaprylin/corn oil, 1/4, v/v) or 100 μ g/g bw, every second week for 8 (8 mice per group) or 16 (18–19 mice per group) weeks.

Aroclor 1254 did not increase the incidence of liver nodules, which were made up of type I, type II, or more commonly a mixture of type I and type II tissues. [The Working Group noted that it was not clear whether the diagnosis referred to hyperplasia and adenoma, respectively.]

[Diwan et al. \(1994\)](#) examined whether Aroclor 1254 promoted NDEA-initiated tumours of the liver in groups of 30 male DBA/2NCr \times C57BL/6NCr (D2B6F1) mice. At age 5 weeks, mice were injected intraperitoneally with NDEA at a dose of 0 (tricaprylin vehicle) or 90 mg/kg bw. At age 7 weeks, mice were fed Aroclor 1254 at a dietary concentration of 175 or 350 mg/kg. The authors estimated the dose to be 0.1 or 0.2 mmol/kg bw per day based on a diet consumption of 4.5 g/day. [It was not reported whether food intake was measured.] Mice were killed after 60 weeks. The incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased in both groups receiving NDEA plus Aroclor 1254 (all tumours were carcinomas) compared with the group receiving NDEA only (all tumours were adenomas). The incidences of hepatoblastoma in the group receiving Aroclor 1254 at 175 mg/kg, and of metaplastic and neoplastic glandular lesions within hepatocellular neoplasms (cholangiocellular neoplasms) in the groups receiving Aroclor 1254 at 175 and 350 mg/kg were higher [$P < 0.01$] than in the group receiving NDEA only.

[Beebe et al. \(1995\)](#) examined the promoting activity of Aroclor 1254 in the lung and liver in three strains of male mice that differ in AhR responsiveness: C57BL/6, DBA/2NCr, and B6D2F1. At age 5 weeks, groups of 23–34 mice were injected intraperitoneally with NDEA at a dose of 0 (tricaprylin vehicle) or 90 mg/kg bw. At age 8 weeks, the mice were placed on a diet containing Aroclor 1254 at a concentration of 0 or 100 mg/kg for 20 weeks. They were then left untreated for 24 weeks until being killed at age 52 weeks. Tumours of the liver were classified as hepatocellular adenoma, hepatocellular

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Aroclor 1254	Mouse, C57BL/6, DBA/2NCR, and B6D2F1 (M) 44 wk Beebe et al. (1995)	<i>Initiation:</i> NDEA (90 mg/kg bw, i.p.) or tricapyrylin vehicle at age 5 wk <i>Promotion:</i> at age 8 wk, Aroclor 1254 (100 mg/kg diet) for 20 wk followed by no-exposure phase of 24 wk Group 1: Tricaprylin Group 2: NDEA Group 3: NDEA+Aroclor 1254 Group 4: Tricaprylin+Aroclor 1254 23–34/group	C57BL/6 Liver tumours (all types): 0/27, 4/28, 19/32*, 2/27 Hepatocellular adenoma: 0/27, 4/28, 17/32**, 2/27 Hepatocellular carcinoma: 0/27, 3/28, 3/32, 0/27 Cholangioadenoma or cholangiocarcinoma (combined): 0/27, 0/28, 4/32, 0/27 Hepatoblastoma: 0/27, 0/28, 4/32, 0/27 Lung tumours (all): 1/27, 20/26, 20/25, 1/27 B6D2F1 Liver tumours (all types): 0/34, 7/33, 8/33, 3/34 Hepatocellular adenoma: 0/34, 6/33, 6/33, 3/34 Hepatocellular carcinoma: 0/34, 0/33, 2/33, 0/34 Cholangioadenoma or cholangiocarcinoma (combined): 0/34, 0/33, 0/33, 0/34 Hepatoblastoma: 0/34, 1/33, 0/33, 0/34 Lung tumours (all): 0/31, 33/34, 31/34, 2/34	* $P < 0.05$ (group 3 vs group 2) ** $P < 0.05$ (group 3 vs group 2 and group 3 vs group 4)	Purity, NR

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Aroclor 1254 (cont.)			DBA/2 Liver tumours (all types): 0/23, 6/28, 6/31***, 0/24 Hepatocellular adenoma: 0/23, 5/28, 4/31, 0/24 Hepatocellular carcinoma: 0/23, 2/28, 2/31, 0/24 Cholangioadenoma or cholangiocarcinoma (combined): 0/23, 0/28, 0/31, 0/24 Hepatoblastoma: 0/23, 0/28, 0/31, 0/24 Lung tumours (all): 3/23, 24/28, 28/29, 1/24	*** <i>p</i> < 0.05 (group 3 vs group 4)	
Aroclor 1254	Mouse, HRS/1 hairless (F) 20 wk Poland et al. (1982)	<i>Initiation</i> : MNNG (5 µmol in 50 µL of acetone) at age 8 wk <i>Promotion</i> : 1 mg Aroclor 1254 in 50 µL of acetone per mouse, twice weekly topically for 20 wk 20 mice in groups receiving Aroclor 1254; 26 in MNNG-only group	Skin papilloma: MNNG + vehicle, 0/23 Vehicle + Aroclor 1254, 0/19 MNNG + Aroclor 1254, 4/19	NS	Statistical test, NR

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Aroclor 1254	Mouse, Swiss (Cr:NIH) (M, F) 44 wk Beebe et al. (1993)	<i>Initiation:</i> For transplacental studies, pregnant mice were injected with NNK (100 mg/kg bw, i.p.) on days 15, 17, and 19 of gestation, or with NDMA (10 mg/kg bw, i.p.) on day 19 of gestation, or with saline vehicle on day 19 of gestation <i>For neonatal studies, pups were injected with NDMA (5 mg/kg bw, i.p.), NNK (50 mg/kg bw, i.p.), or saline vehicle on PND 4</i> <i>Promotion:</i> Aroclor 1254 (500 mg/kg bw, p.o.) or olive oil vehicle on PND 56 <i>Transplacental initiation</i> Group 1: Saline/olive oil Group 2: Saline/Aroclor 1254 Group 3: NDMA/olive oil Group 4: NDMA/Aroclor 1254 Group 5: NNK/olive oil Group 6: NNK/Aroclor 1254 <i>Neonatal initiation</i> Group 7: NDMA/olive oil Group 8: NDMA/Aroclor 1254 Group 9: NNK/olive oil Group 10: NNK/Aroclor 1254 Animals/group, NR	<i>Transplacental initiation</i> Lung tumours (M): 2/27, 3/30, 0/29, 10/28*, 1/27, 8/29** Lung tumours (F): 1/29, 2/30, 3/30, 4/30, 4/30, 5/29 <i>Neonatal initiation</i> Lung tumours (M): 11/28, 22/30***, 8/30, 10/30 Lung tumours (F): 16/27, 19/27, 4/30, 11/29****	* $P < 0.001$ (group 4 vs group 3) ** $P = 0.026$ (group 6 vs group 5) *** $P = 0.016$ (group 8 vs group 7) **** $P = 0.039$ (group 10 vs group 9)	Purity, NR The classification of lung tumours was not provided
Aroclor 1254	Rat, Sprague-Dawley (M) 18 wk Preston et al. (1981)	<i>Initiation:</i> NDEA at 66 µg/mL in drinking-water for 5 wk <i>Promotion:</i> Aroclor 1254 or Aroclor 1254 from which PCDFs were removed at 100 mg/kg diet, or control diet 40/group	Hepatocellular carcinoma: NDEA alone, 5/32 NDEA + Aroclor 1254, 21/33* NDEA + Aroclor 1254 with PCDFs removed, 27/32*	* $P < 0.05$, χ^2 analysis	
Aroclor 1254	Rat, Sprague-Dawley (M) 19 wk Vansell et al. (2004)	<i>Initiation:</i> DIPN (2.5 g/kg bw, s.c.) <i>Promotion:</i> 1 wk later, Aroclor 1254 at 100 mg/kg diet for 19 wk 24/group	<i>Thyroid</i> Cystic adenoma: 0/24, 2/22 Follicular adenoma: 5/24, 9/22 Follicular carcinoma: 1/24, 0/22 "Complete carcinoma": 0/24, 4/22*	* $P < 0.05$	Uncertainty in classification of one type of thyroid tumour as "complete carcinoma"

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Kanechlor 400	Rat, Donryu (F) 6 mo Kimura et al. (1976)	<i>Initiation:</i> MDAB (600 mg/kg diet) for 2 mo, rats aged 11–15 wk <i>Treatment:</i> with Kanechlor 400 at 400 mg/kg diet before, during, or after MDAB Two groups were treated with Kanechlor 400 or MDAB only 25/group; 10 untreated controls	Hepatocellular carcinoma: MDAB alone, 2/15 MDAB followed by Kanechlor 400, 7/11* Kanechlor 400 followed by MDAB, 0/9 MDAB/Kanechlor 400 together, 0/11 Kanechlor 400 alone, 0/12 Untreated controls, 0/7	[* $P < 0.05$] vs MDAB-only group	The authors indicated that the incidence in the group receiving MDAB followed by Kanechlor 400 was significantly different from that in all other groups, using <i>t</i> -test, but the Working Group noted that this test cannot be used for binomial data
Kanechlor 500	Rat, Wistar (M) 40 or 52 wk Nishizumi (1979)	<i>Initiation:</i> NDEA at 50 mg/L in drinking-water for 2 wk <i>Promotion:</i> 1 wk later, 0.1 mL of 10% Kanechlor 500 in olive oil, by gavage, twice per week for 12 wk, then maintained until 40 or 52 wk after start of study 7–8/group per time-point	Hepatocellular tumours (mainly carcinomas): 40 wk: NDEA + olive oil: 0/8 NDEA + Kanechlor 500: 6/7* (3.3 tumours/rat)** 52 wk: NDEA + olive oil: 0/8 NDEA + Kanechlor 500: 8/8* (6.9 tumours/rat)**	*[$P < 0.05$] ** $P < 0.01$	
Unspecified PCB mixture	Rat, F344 (M) 32 wk Hirose et al. (1981)	<i>Initiation:</i> 0.1% EHEN in drinking-water for 2 wk <i>Promotion:</i> 0 or 0.05% unspecified PCB mixture in diet for 32 wk UN 1 wk after starting PCBs 20–21/group	Hepatocellular carcinoma: EHEN only, 7/21 EHEN + PCB, 19/19 Renal cell tumours [benign]: EHEN, 18/21 EHEN + PCB, 12/19	$P < 0.001$ NS	PCB mixture: Kanegafuchi Chemical Co., Osaka, Japan No renal cell carcinomas were observed Statistical analysis, NR

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Unspecified PCB mixture	Rat F344 (M) 32 wk Arai et al. (1983)	<i>Initiation:</i> NDMA (0.04% in diet) for 2 wk <i>Promotion:</i> 2 wk later, 500 mg/kg diet PCB mixture (or a basal diet) for 28 wks; UN 1 wk after starting PCBs 20/group	<i>Liver</i> Hyperplastic or neoplastic nodules (combined): NDMA, 5/18 NDMA + UN, 7/20 NDMA + PCBs, 10/11* NDMA + PCBs + UN, 7/7* <i>Hepatocellular carcinoma:</i> NDMA, 0/18 NDMA + UN, 0/20 NDMA + PCBs, 3/11* NDMA + PCBs + UN, 1/7 <i>Kidney</i> Nephroblastoma: NDMA, 17/18 NDMA + UN, 18/20 NDMA + PCBs**, 4/11 NDMA + PCBs + UN**, 3/7	*[P < 0.05] vs control group **[P < 0.05] vs control group (decrease)	PCB mixture: Kanegafuchi Chemical Co., Osaka, Japan Statistical analysis, NR Significant mortality in some groups, especially in the group receiving NDMA + PCBs + UN
<i>PCBs with other modifying agents</i>					
Aroclor 1254	Mouse, C57BL/10ScSn and DBA/2 2, 4, 8, and 12 mo Smith et al. (1990)	Injection with Fe (Fe-dextran, 12 mL/kg; Fe, 600 mg/kg bw, s.c.) or dextran followed 7 days later by Aroclor 1254 at 100 mg/kg diet for 2 mo (5 mice/group), 4 mo (C57 only, 5 mice/group), 8 mo (10 mice/group for C57; 5–7 group for DBA), or 12 mo (C57 only, 15–19/group)	<i>Hepatocellular adenoma:</i> 4 mo: Aroclor 1254, 0/5 Aroclor 1254 + Fe, 1/5 8 mo (C57): Aroclor 1254, 0/10 Aroclor 1254 + Fe, 7/9* 12 mo: Aroclor 1254, 0/16 Aroclor 1254 + Fe, 15/18* <i>Hepatocellular carcinoma:</i> 12 mo only: Aroclor 1254, 1/16 Aroclor 1254 + Fe, 7/18*	*[P < 0.05]	Statistical analysis, NR No effects of iron and Aroclor 1254 in DBA/2 mice

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Aroclor 1254	Mouse, C57BL/10ScSn 8 and 12 mo Smith et al. (1995)	Injection with Fe-dextran (Fe, 600 mg/kg bw, s.c.) or dextran, followed 3 days or 1 wk later by Aroclor 1254 at 100 mg/kg diet; for 8 mo (10/group) or 12 mo (15–19/group) Group 1: Aroclor Group : Aroclor + Fe	8 mo: Group 1: 0/10 (hepatocellular tumours); Group 2: 7/9* (hepatocellular adenoma) 12 mo: Group 1: 0/16 (hepatocellular tumours); Group 2: 15/18* (hepatocellular adenoma) and 7/18* (hepatocellular carcinoma)	*[$P < 0.05$]	Statistical analysis, NR
Aroclor 1254	Mouse, C57BL/6J (M), <i>Cyp1a2^{+/-}</i> or ^{+/+} (wildtype) 57 wk Greaves et al. (2005)	Injection with Fe-dextran (Fe, 800 mg/kg bw; route NR) followed by Aroclor 1254 at 100 mg/kg diet for 57 wk Fe + Aroclor 1254, 10/group Fe-only, 5/group Greaves et al. (2005)	Liver adenoma: Fe-only: <i>Cyp1a2^{+/-}</i> : 0/5 <i>Cyp1a2^{-/-}</i> : 0/5 Fe + Aroclor: <i>Cyp1a2^{+/-}</i> : 5/10* <i>Cyp1a2^{-/-}</i> : 0/10	*[NS]	Statistical analysis, NR
Kanechlor 400	Mouse, A/J (M) 24 wk Nakanishi et al. (2001)	Single dose of Kanechlor 400 (2.5 mg/kg bw; i.p.) or DMSO vehicle injected into mice aged 6 wk. Mice were then injected with 1-nitropyrene at 1575 mg/kg bw (total dose of all injections) or DMSO vehicle (i.p., 3×/wk), 17 injections. Mice killed 18 wk after final injection of 1-nitropyrene 8–20/group	<i>Bronchioloalveolar lesions</i> Incidence (average number): DMSO control: 0/8 (0) Kanechlor 400: 2/10 (0.4) 1-Nitropyrene: 16/20 (1.8) Kanechlor 400 + 1-nitropyrene: 13/13 (3.2)* Number: DMSO control: 0 Kanechlor 400: 2 hyperplasias, 2 adenomas; 1-Nitropyrene: 10 hyperplasias, 20 adenomas, 3 adenocarcinomas; 1-Nitropyrene + Kanechlor 400: 15 hyperplasias, 23 adenomas, 8 adenocarcinomas	* $P < 0.01$ compared with 1-nitropyrene group	Statistical analysis, NR for incidence and number of lesions

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Kanechlor 400 and Kanechlor 500	Mouse, dd (M) 24 wk Nagasaki et al. (1975)	Dietary administration for 24 wk: α-BHC (250 mg/kg) α-BHC (250 mg/kg) + Kanechlor 500 (250 mg/kg) α-BHC (250 mg/kg) + Kanechlor 400 (250 mg/kg) α-BHC (100 mg/kg) α-BHC (100 mg/kg) + Kanechlor 500 (250 mg/kg) α-BHC (100 mg/kg) + Kanechlor 500 (100 mg/kg) α-BHC (100 mg/kg) + Kanechlor 400 (250 mg/kg) α-BHC (100 mg/kg) + Kanechlor 400 (100 mg/kg) α-BHC (50 mg/kg) α-BHC (50 mg/kg) + Kanechlor 500 (250 mg/kg) α-BHC (50 mg/kg) + Kanechlor 500 (100 mg/kg) α-BHC (50 mg/kg) + Kanechlor 400 (250 mg/kg) α-BHC (50 mg/kg) + Kanechlor 400 (100 mg/kg) Kanechlor 500 (250 mg/kg) Kanechlor 500 (100 mg/kg) Kanechlor 400 (250 mg/kg) Kanechlor 400 (100 mg/kg) 20–38/group	<i>Liver</i> Nodular hyperplasia: 30/38, 16/20, 26/30, 0/20, 8/25, 3/24, 4/29, 0/27, 0/20, 9/30, 0/28, 0/28, 0/27, 0/20, 0/20, 0/20, 0/20 Hepatocellular carcinoma: 10/38, 11/20*, 15/30*, 0/20, 1/25, 0/24, 0/29, 0/27, 0/20, 2/30, 0/28, 0/28, 0/27, 0/20, 0/20, 0/20, 0/20	*[$P < 0.05$] compared with α-BHC (250 mg/kg) group	The chemical is erroneously reported as benzene hexachloride and is actually hexachlorocyclohexane Statistical analysis, NR

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Kanechlor 500	Mouse, dd (M) 24 wk Ito et al. (1973)	BHC, (α , β , or γ isomers) (50, 100 or 250 mg/kg diet) for 24 wk \pm Kanechlor 500 (250 mg/kg diet) for 24 wk 25–30/group	<i>Liver nodular hyperplasia</i> α -BHC: 0/28, 0/26, 23/30 α -BHC + Kanechlor 500: 9/30, 8/25*, 21/26 β -BHC: 0/28, 0/26, 0/26 β -BHC + Kanechlor 500: 0/29, 5/30*, 16/29* <i>Hepatocellular carcinoma</i> α -BHC: 0/28, 0/26, 8/30 α -BHC + Kanechlor 500: 2/30, 1/25, 15/26* β -BHC: 0/28, 0/26/, 0/26 β -BHC + Kanechlor 500: 0/29, 1/30, 6/29* γ -BHC (all doses) and γ -BHC (all doses) + Kanechlor 500: no tumours (0/26–30)	*[$P < 0.05$]	The chemical is erroneously reported as benzene hexachloride and is actually hexachlorocyclohexane Statistical analysis, NR
PCB-77	Rat, Sprague-Dawley (F) 10.5 wk Nesaretnam et al. (1998)	Single dose of DMBA at 10 mg by gavage in 0.5 mL corn oil at age 50 days PCB-77 treatment: single dose at 10 mg/kg bw by gavage at the same time as DMBA, then in the diet at 500 mg/kg for one additional wk ($n = 2 \times 20$); or DMBA only ($n = 2 \times 20$) Rats were then fed either a low-fat (5%) ($n = 2 \times 20$) or a high-fat (20%) diet ($n = 2 \times 20$) Total: 4 groups of 20 rats Group 1: DMBA+PCB-77 + low fat Group 2: DMBA+PCB-77 + high fat Group 3: DMBA + low fat Group 4: DMBA + high fat	Mammary gland tumours (mainly mammary ductal carcinoma) no tumours (0/26–30)	Number of palpable tumours: $P < 0.005$ for group 2 vs group 4 and group 1 vs group 3 at 8, 9, and 10 wk Incidence at 10.5 wk: $P < 0.05$ for group 1 (60%) vs group 3 (15%)	It was unclear whether the rats not treated with PCB-77 were given the vehicle instead Data were presented graphically

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
PCB-126, PeCDF, and TCDD	Rat, Harlan Sprague-Dawley (F) 104 wk NTP (2006c)	PCB-126, TCDD and PeCDF in corn oil : acetone (99 : 1) by gavage 5 days/wk for 104 wk at doses of: 0 ng TEQ/kg bw (controls); 10 ng TEQ/kg bw (3.3 ng/kg TCDD, 6.6 ng/kg PeCDF, 33.3 ng/kg PCB 126); 22 ng TEQ/kg bw (7.3 ng/kg TCDD, 14.5 ng/kg PeCDF, 73.3 ng/kg PCB 126); 46 ng TEQ/kg bw (15.2 ng/kg TCDD, 30.4 ng/kg PeCDF, 153 ng/kg PCB-126); and 100 ng TEQ/kg bw (33 ng/kg TCDD, 66 ng/kg PeCDF, 333 ng/kg PCB 126) 81 rats/group Interim evaluations: up to 10 rats/group were evaluated at 14, 31, and 53 wk	<i>Liver</i> Hepatocellular adenoma: 0/53, 1/53, 1/53, 1/53, 11/51* Cholangiocarcinoma: 0/53, 0/53, 2/53, 7/53*, 9/51** <i>Lung</i> Cystic keratinizing epithelioma: 0/53, 0/53, 0/53, 2/53, 20/53*	*P < 0.001 P < 0.001 (trend) *P = 0.011 **P < 0.001 P < 0.001 (trend) *P < 0.001 P < 0.001 (trend)	<i>Non-neoplastic lesions</i> Liver: hepatocyte hypertrophy, multinucleated hepatocytes, pigmentation, inflammation, diffuse fatty change, bile duct hyperplasia, oval cell hyperplasia, eosinophilic focus, cholangiofibrosis, bile duct cysts, necrosis, portal fibrosis, mixed cell focus, and toxic hepatopathy Lung: squamous metaplasia

DIPN, *N*-nitroso diisopropanolamine; DMBA, 7,12-dimethylbenz[*a*]anthracene; EHEN, *N*-ethyl-*N*-hydroxyethylnitrosamine; i.p., intraperitoneal; MDAB, 3'-methyl-4-dimethylaminoazobenzene; MNNG, *N*-methyl-*N*'-nitrosoguanidine; mo, month; MNU, *N*-methyl-*N*-nitrosourea; NDEA, *N*-nitrosodiethylamine; NDMA, *N*-nitrosodimethylamine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; NR, not reported; NS, not significant; PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran; PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; s.c., subcutaneous; TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; UN, unilateral nephrectomy; wk, week

carcinoma, cholangioadenoma, cholangiocarcinoma, or hepatoblastoma. [The classification of tumours of the lung was not described.] In NDEA-treated DBA/2NCR mice and B6D2F1 mice, Aroclor 1254 did not affect the incidence or multiplicity of tumours of the liver (all or any of the various types) when compared with mice receiving NDEA only. In NDEA-treated C57BL/6 mice, Aroclor 1254 increased the incidences of tumours of the liver (all types combined) and of hepatocellular adenoma. The incidence or multiplicity of tumours of the lung was not affected by treatment with NDEA and Aroclor 1254 in any strain when compared with mice receiving NDEA only.

[Poland *et al.* \(1982\)](#) investigated whether Aroclor 1254 could promote *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG)-initiated skin papillomas in female HRS/1 hairless mice. At age 8 weeks, mice were given 5 µmol of MNNG (in 50 µl of acetone) or the vehicle topically. Mice were then given a topical application of 1 mg of Aroclor 1254 (in 50 µl of acetone) per mouse, twice per week, for 20 weeks. There were 20 mice in the groups receiving MNNG plus Aroclor 1254, or Aroclor 1254 only, and 26 in the MNNG only-treated group. Aroclor 1254 did not promote MNNG-initiated tumours, and there was no neoplastic effect of Aroclor 1254 in non-initiated mice. [The statistical test was not reported.]

[Beebe *et al.* \(1993\)](#) investigated whether Aroclor 1254 could promote tumours of the lung and liver initiated by NDMA or 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), either neonatally or transplacentally, in male and female Swiss (Cr:NIH) mice. For transplacental studies, pregnant mice were injected intraperitoneally with NNK at a dose of 0 (saline vehicle) or 100 mg/kg bw on days 15, 17, and 19 of gestation, or with NDMA at a dose of 0 (saline vehicle) or 10 mg/kg bw on day 19 of gestation. For the neonatal studies, infant mice were injected with NDMA (5 mg/kg bw), NNK (50 mg/kg bw), or saline vehicle on postnatal day 4. Mice were then

given Aroclor 1254 by gavage (500 mg/kg bw) or olive oil vehicle for 44 weeks starting at age 56 days. There were 27–30 mice in all groups when the mice were killed at age 52 weeks. In females, transplacental exposure to NNK or NDMA plus Aroclor 1254 did not increase the incidence of tumours of the lung or liver compared with controls treated with NNK or NDMA only. In males, Aroclor 1254 increased the incidence of tumours of the lung (but not of the liver) initiated by either NDMA or NNK transplacentally. In females, Aroclor 1254 increased the incidence of tumours of the lung initiated neonatally by NNK, but not by NDMA. In males, Aroclor 1254 increased the incidence of tumours of the lung initiated neonatally by NDMA, but not by NNK. [The classification of tumours of the lung was not provided.]

(ii) *Rat*

[Preston *et al.* \(1981\)](#) investigated whether Aroclor 1254 promotes chemically-induced hepatocarcinogenesis in male Sprague-Dawley rats. Three groups of 40 rats were first given drinking-water containing NDEA at a concentration of 66 µg/mL for 5 weeks as an initiating agent. The rats were then fed an unrefined diet containing Aroclor 1254 at a concentration of 100 mg/kg, or Aroclor 1254 from which PCDFs (present as impurities) had been removed, or control diet. Rats were fed the diets for 18 weeks and then killed. Lesions of the liver were classified as foci of cellular alteration, neoplastic nodules, hepatocellular carcinoma, cholangioma, or cholangiocarcinoma. The administration of either Aroclor 1254, or Aroclor 1254 without PCDFs, significantly increased the incidences of NDEA-initiated hepatocellular carcinoma.

[Vansell *et al.* \(2004\)](#) studied whether Aroclor 1254 could promote tumours of the thyroid initiated by *N*-nitrosodiisopropanolamine (DIPN) in male Sprague-Dawley rats. Rats were first injected subcutaneously with DIPN at 0 (saline) or 2.5 g/kg bw. After a 1-week recovery period,

rats were fed a diet containing Aroclor 1254 at a concentration of 100 mg/kg for 19 weeks and then killed. Tumours were classified as thyroid cystic adenoma, thyroid follicular adenoma, thyroid follicular carcinoma, or “thyroid complete carcinoma.” Aroclor 1254 only significantly increased the incidence of “thyroid complete carcinoma.” [The Working Group noted the uncertainty of the classification of one type of thyroid tumour as “thyroid complete carcinoma.”]

(c) *Kanechlor 400 and Kanechlor 500*

Rat

[Kimura et al. \(1976\)](#) gave female Donryu rats (age, 11–15 weeks) diets containing Kanechlor 400 or 3'-methyl-4-dimethylaminoazobenzene (MDAB) at a concentration of 400 or 600 mg/kg, respectively. Both agents were dissolved in olive oil before being added to the diet. There were five groups of 25 rats each. A first group was treated with Kanechlor 400 for 6 months, no treatment for 2 months, and then MDAB for 2 months; a second group was treated with MDAB for 2 months, no treatment for 2 months, then Kanechlor 400 for 6 months; a third group was treated with Kanechlor 400 for 6 months with MDAB given for the last 2 months, and no treatment for 4 months; a fourth group was treated with MDAB for 2 months and no treatment for 8 months; and a fifth group treated with Kanechlor 400 for 6 months and no treatment for 4 months. Additionally a sixth group of 10 rats was maintained for 10 months with no treatment. In all groups except that given MDAB only, body weight decreased markedly compared with untreated controls. Therefore, treatment with Kanechlor 400 was discontinued for 2 weeks after 3 months of treatment, and again for 4 weeks after the second 1 month of treatment. As for survival, 9, 11, 11, 15, 12 and 7 mice remained in groups 1 to 6, respectively. Only 2 out of 15 mice receiving MDAB only developed hepatocellular carcinoma compared with 7 out of 11

mice receiving MDAB followed by Kanechlor 400 [$P < 0.05$]. [The Working Group noted that the authors calculated the incidence in the group receiving MDAB then Kanechlor 400 compared to all other groups using a *t*-test, but it is not correct to use this test for binomial data.]

In a study to determine whether Kanechlor 500 could promote NDEA-initiated carcinogenesis, groups of 7–8 male Wistar rats were given drinking-water containing NDEA at a concentration of 50 mg/L for 2 weeks ([Nishizumi, 1979](#)). After a 1-week recovery period, the rats were given Kanechlor 500 (0.1 mL of 10% Kanechlor 500 in olive oil) by gavage twice per week for 12 weeks. Rats were then maintained without further treatment until being killed 40 and 52 weeks after the start of the experiment. Data were analysed using the Student *t*-test. The incidence [$P < 0.05$] and tumour multiplicity ($P < 0.01$) of hepatocellular tumours (mainly hepatocellular carcinomas) was significantly higher in rats given NDEA plus Kanechlor 500 than in rats given NDEA only, at both 40 and 52 weeks.

(d) *Unspecified PCBs*

Rat

In a study to examine the effect of an unspecified PCB mixture on hepatic and renal carcinogenesis induced by *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN), two groups of 20–21 male Fischer 344 rats were given drinking-water containing 0.1% EHEN for 2 weeks, or untreated drinking-water ([Hirose et al., 1981](#)). After an unspecified time, rats were placed on a diet containing 0.05% PCBs [not further specified] for 32 weeks. One week after starting the experimental diet, the right kidney was removed (unilateral nephrectomy). All rats treated with EHEN plus PCBs (19 out of 19; $P < 0.001$) developed hepatocellular carcinoma, compared with one third (7 out of 21) of the rats treated with EHEN only. Treatment with PCBs had no effect on the incidence or number of EHEN-induced

tumours of the kidney (neoplastic nodules or renal cell tumours [all benign tumours]) compared with rats receiving EHEN only. No renal cell carcinoma was observed.

In a study to determine whether an unspecified PCB mixture could promote tumours of the liver and kidney induced by NDMA, four groups of 20 male Fischer 344 rats were fed a diet containing 0.04% NDMA for 2 weeks ([Arai et al., 1983](#)). After a 2-week recovery period, rats were fed a diet containing PCBs [not further specified] at a concentration of 0 (basal diet) or 500 mg/kg for 28 weeks and then killed. In some groups, unilateral nephrectomy was performed at 5 weeks (1 week after starting the PCB containing diet). Tumours of the liver were classified as hyperplastic and neoplastic nodules, and hepatocellular carcinoma. Tumours of the kidney were classified as adenoma, adenocarcinoma, and nephroblastoma. In rats receiving NDMA plus PCBs, the incidences of liver hyperplastic or neoplastic nodules (combined) and of hepatocellular carcinoma (only in non-nephrectomized rats) were higher than in the respective controls. The administration of PCBs, either with or without nephrectomy, decreased the incidence of nephroblastoma. [The Working Group noted that no statistical analysis was reported and that there appeared to be significant mortality in some groups, especially in the group receiving NDMA plus PCBs plus unilateral nephrectomy.]

3.3.2 Studies with other modifying agents

(a) PCB-77

Rat

[Nesaretnam et al. \(1998\)](#) investigated whether dietary fat could influence the effect of PCB-77 on DMBA-induced tumours of the mammary gland in female Sprague-Dawley rats. Groups of 20 female rats were given DMBA (10 mg in 0.5 mL corn oil) by gavage at age 50 days. Two groups were also given a simultaneous dose of PCB-77

at 10 mg/kg bw by gavage, then a diet containing PCB-77 at a concentration of 500 µg/g corn oil for an additional week. Two groups were not exposed to PCB-77. [It was unclear whether these rats were given the vehicle instead of PCB-77.] The four groups (treated and not treated with PCB-77) were then fed either a low-fat (5%) or a high-fat (20%) purified diet. [Fat was substituted for dextrose on a weight basis rather than on a caloric basis.] Rats were palpated weekly for tumours of the mammary gland and were killed 10.5 weeks after administration of DMBA. Tumours at autopsy were mainly classified as mammary ductal carcinoma. The number of palpable tumours of the mammary gland was significantly higher in rats fed a high-fat diet plus PCB-77 than in rats fed a high-fat diet only, at 8, 9, and 10 weeks. Similarly, the incidence of tumours of the mammary gland was higher in rats fed a low-fat diet plus PCB-77 (~60%) than in rats fed a low-fat diet (~15%) only, at 10.5 weeks. [Data were presented graphically.]

(b) Aroclor 1254

Mouse

[Smith et al. \(1990\)](#) investigated whether iron (Fe) and/or Aroclor 1254 could influence liver carcinogenesis in male C57BL/10ScSn and DBA/2 mice. Mice (age 7–10 weeks) were first injected subcutaneously with Imferon, an Fe–dextran complex (12 mL/kg; dose of Fe, 600 mg/kg bw) or an equivalent volume of dextran C solution in water (200 mg/mL). After 7 days, mice were fed a diet mixed with 2% corn oil containing Aroclor 1254 at a concentration of 100 mg/kg for 2 (5 mice/group), 4 (C57 only, 5 mice/group), 8 (C57, 10 mice/group; DBA, 5–7 mice/group), or 12 months (C57 only, 15–19 mice/group) before being killed. Tumours were classified as hepatocellular adenoma or hepatocellular carcinoma. Higher incidences of hepatocellular tumour were observed in C57 mice receiving both Fe and Aroclor 1254 at 8 months (adenomas) and 12

months (adenomas and carcinomas) compared with those receiving Aroclor 1254 only. [No statistical analyses were reported.]

[Smith et al. \(1995\)](#) studied the influence of Fe and/or Aroclor 1254 on liver carcinogenesis in male C57BL/10ScSn mice [age of mice not reported]. Mice were subcutaneously injected a Fe–dextran solution (100 mg/mL Fe, and 100 mg/mL dextran; dose of Fe, 600 mg/kg bw) or the equivalent dextran solution only. After 3 days or 1 week, mice were fed a diet containing Aroclor 1254 (0.01% of diet) and corn oil (2%) for 8 months (10 mice/group) or 12 months (15–19 mice/group). Tumours were classified as nodules [hepatocellular adenoma] or hepatocellular carcinoma. Higher incidences of hepatocellular tumours were observed in mice receiving Aroclor 1254 plus Fe for 8 months (adenomas) and 12 months (adenomas and carcinomas) than in mice receiving Aroclor 1254 only. [No statistical analyses were reported.]

[Greaves et al. \(2005\)](#) studied the effects of deletion of the *Cyp1a2* gene on the induction of tumours of the liver by Aroclor 1254 and Fe in male C57BL/6J mice. *Cyp1a2* knockout ($^{-/-}$) and wildtype ($^{+/+}$) mice were given a Fe–dextran solution (Fe, 800 mg/kg bw) [route not reported], followed by a diet containing Aroclor 1254 at 100 mg/kg for 57 weeks or until death. There were 10 mice in the Aroclor 1254-treated groups and 5 mice in the control groups receiving Fe only. Liver tumours were classified as adenomas. No tumours were observed in *Cyp1a2* ($^{-/-}$) mice or in *Cyp1a2* ($^{+/+}$) wildtype mice not receiving Aroclor 1254. No tumours were seen in the 10 *Cyp1a2* ($^{-/-}$) mice receiving Aroclor 1254, but 5 out of 10 [not significant] of the wildtype mice receiving Aroclor 1254 developed liver adenoma. [No statistical analyses were provided.]

(c) *Kanechlor 400 and Kanechlor 500*

Mouse

[Nakanishi et al. \(2001\)](#) examined the effects of Kanechlor 400 on lung tumorigenesis induced by 1-nitropyrene in male A/J mice. Mice (age, 6 weeks) were given a single intraperitoneal dose of Kanechlor 400 at 0 (corn oil vehicle) or 2.5 mg/kg bw. Mice were then given 1-nitropyrene or the DMSO vehicle, three times per week (17 intraperitoneal injections for a total dose of 1575 mg/kg bw). Mice were killed 18 weeks after the last injection of 1-nitropyrene. Numbers of mice per group were as follows: DMSO controls, 8; Kanechlor 400, 10; 1-nitropyrene, 20; 1-nitropyrene plus Kanechlor 400, 13. Lung lesions were classified as bronchioloalveolar hyperplasia, adenoma, or adenocarcinoma. The incidence of lesions of the lung was increased in both groups of mice receiving 1-nitropyrene. The average number of lesions, but not incidence, was significantly greater in the group receiving Kanechlor 400 plus 1-nitropyrene than in the group receiving 1-nitropyrene only.

[Nagasaki et al. \(1975\)](#) investigated whether co-administration of Kanechlor 400 or Kanechlor 500 and α -benzene hexachloride (α -BHC) [hexachlorocyclohexane] would affect the incidence of nodular hyperplasia of the liver and hepatocellular carcinoma in male dd mice. Mice were given diets containing α -BHC at a concentration of 50, 100, or 250 mg/kg, and/or Kanechlor 400 or Kanechlor 500 (100 or 250 mg/kg), for 24 weeks. Nodular hyperplasia and hepatocellular carcinoma were observed. The incidence of hepatocellular carcinoma was higher [$P < 0.05$] in mice receiving 250 mg/kg α -BHC and the higher dose of Kanechlor 400 or Kanechlor 500, than in mice receiving only α -BHC at 250 mg/kg. No tumours were induced by Kanechlor 400 or Kanechlor 500 only. [Statistical analyses were not reported.]

A study by [Ito et al. \(1973\)](#) examined the effects of co-administration of Kanechlor 500 and one isomer of benzene hexachloride (BHC)

[hexachlorocyclohexane] on the incidence of nodular hyperplasia of the liver and hepatocellular carcinoma. Groups of male dd mice (age, 8 weeks) were given diets containing α -, β -, or γ -BHC (50, 100 or 250 mg/kg) for 24 weeks, with or without Kanechlor 500 (250 mg/kg). In some groups, Kanechlor 500 promoted the incidence of nodular hyperplasia and hepatocellular carcinoma induced by α -BHC and β -BHC. [Statistical analyses were not reported.]

(d) PCB-126, PeCDF, and TCDD

Rat

In a study by the NTP, groups of 81 female Harlan Sprague-Dawley rats were given a mixture of TCDD, PeCDF, and PCB-126 by gavage, 5 days per week, for up to 2 years (NTP, 2006e). Up to 10 rats per group were evaluated after 14, 31, and 53 weeks. Doses were formulated by using the WHO TEF values of 1.0 for TCDD, 0.1 for PCB-126, and 0.5 for PeCDF. Specific target doses were: “10 ng TEQ/kg bw” (TCDD, 3.3 ng/kg; PeCDF, 6.6 ng/kg; PCB-126, 33.3 ng/kg), “22 ng TEQ/kg bw” (TCDD, 7.3 ng/kg; PeCDF, 14.5 ng/kg; PCB-126, 73.3 ng/kg), “46 ng TEQ/kg bw” (TCDD, 15.2 ng/kg; PeCDF, 30.4 ng/kg; PCB-126, 153 ng/kg), and “100 ng TEQ/kg bw” (TCDD, 33 ng/kg; PeCDF, 66 ng/kg; PCB-126, 333 ng/kg). Rats in the control group received the corn oil : acetone vehicle (99 : 1; 2.5 mL/kg bw) only. After 2 years, there were statistically significant increases ($P < 0.001$) in the incidences of cholangiocarcinoma, hepatocellular adenoma, and cystic keratinizing epithelioma of the lung in the group at 100 ng TEQ/kg bw. The incidence of cholangiocarcinoma was also significantly increased ($P = 0.011$) in the group at 46 ng TEQ/kg. In addition, there was a significant trend in the incidence of these three types of neoplasm with increasing dose.

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