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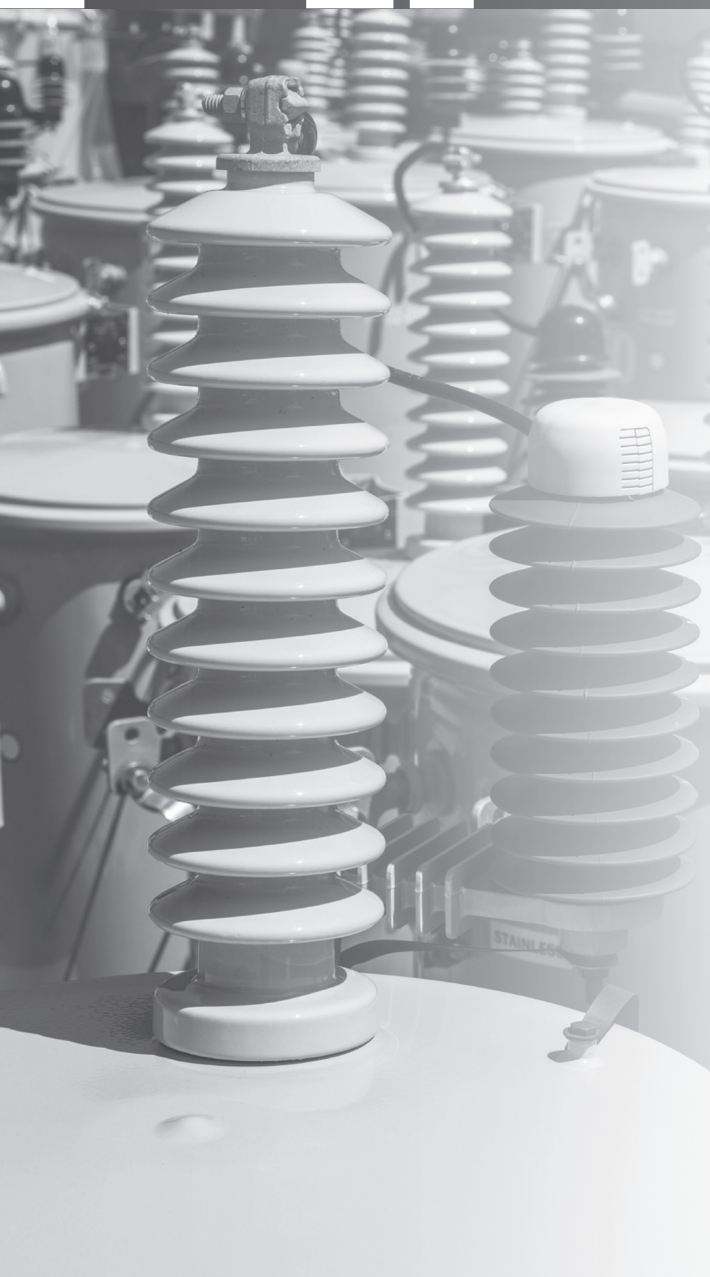

POLYCHLORINATED BIPHENYLS AND POLYBROMINATED BIPHENYLS

VOLUME 107

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International Agency for Research on Cancer

World Health Organization

POLYBROMINATED BIPHENYLS

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1. Exposure Data

1.1 Identification of the agents

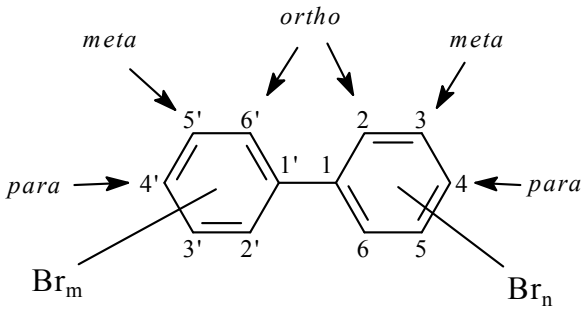
The terms "polybrominated biphenyls" or "polybromobiphenyls" (PBBs) refer to a group of halogenated hydrocarbons that are formed by substituting hydrogen with bromine on a biphenyl ring. PBBs have a molecular formula of $C_{12}H_{(10-n-m)}Br_{(n+m)}$ where n + m = 1 to 10, i.e. from monobromobiphenyl to decabromobiphenyl.

There are 209 possible structural congeners of the brominated biphenyl structure containing one or more bromines; however, only a few of these have been synthesized individually and characterized (Stepniczka, 1976; Sundström *et al.*, 1976a). The number of PBB congeners that actually exist in commercial mixtures is much lower than that of polychlorinated biphenyls (PCB) congeners.

Like for PCBs, positions 2, 2′, 6, and 6′ are called *ortho* positions, positions 3, 3′, 5, and 5′ are called *meta* positions, and positions 4 and 4′ are called *para* positions (Fig. 1.1).

The benzene rings can rotate around the 1,1′ carbon bond. The two theoretical extreme configurations are planar (angle = 0°) and perpendicular (the two benzene rings are in perpendicular planes). The degree of planarity is largely determined by the number of substitutions in the *ortho* positions. Since bromine atoms are more bulky than chlorine atoms, substitution in *ortho* positions for PBBs is much less favoured than for PCBs. The replacement of hydrogen atoms in the *ortho* positions with bromine atoms forces the benzene rings to adopt a configuration with a larger angle. The benzene rings of non-*ortho* as well as mono-*ortho* substituted PBBs adopt a small angle so that the configuration is nearly planar (Fig. 1.2).

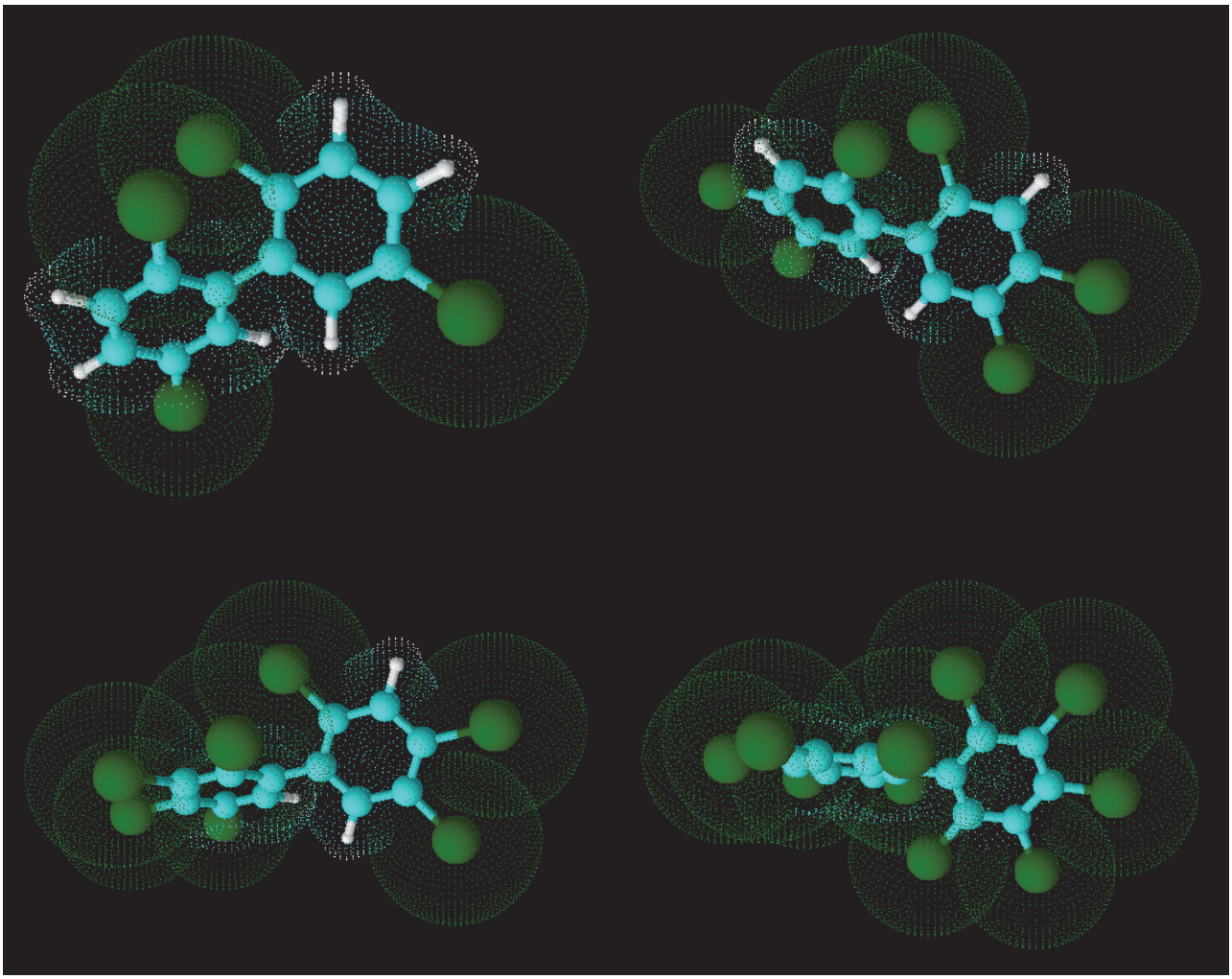
Fig. 1.1 Chemical structure of polybrominated biphenyls and the IUPAC numbering system



Hydrogen atoms in positions 2,2′,6,6′ (*ortho*), 3,3′,5,5′ (*meta*) and/or 4,4′ (*para*) may be substituted by bromine atoms; n+m = 1–10
IUPAC, International Union of Pure and Applied Chemistry
Compiled by the Working Group

The numbering of PBBs from 1 to 209 corresponds to the scheme developed for PCBs by Ballschmiter & Zell (1980) and updated in Ballschmiter *et al.* (1992), i.e. in ascending numerical order, which generally follows the rules of the International Union of Pure and Applied Chemistry (IUPAC) for substituent characterization of biphenyls (rule A-52.3 related to hydrocarbon systems) (Table 1.1). This numbering system, referred to as BZ numbering, is widely used for identifying

Fig. 1.2 Tridimensional chemical structures of PBBs



Spatial configurations of three mono-*ortho* PBBs, e.g. PBB-52 (2,2′,5,5′-tetraBB, up and left), PBB-153 (2,2′,4,4′,5,5′-hexaBB, up and right), and PBB-180 (2,2′,3,4,4′,5,5′-heptaBB, down and left), and non-coplanar configuration of one di-*ortho* PBB, e.g. PBB-209 (2,2′,3,3′,4,4′,5,5′,6,6′-decaBB, down and right)
BB, brominated biphenyl; PBBs, polybrominated biphenyls
Courtesy of Professor B. LeBizec

Table 1.1 BZ number and correspondence between the positions of bromine atoms on each phenyl ring of the PBBs (nomenclature according to Ballschmiter *et al.*, 1992)[a]

Position of bromine atom on each ring	2	3	4	2,3	2,4	2,5	2,6	3,4	3,5	2,3,4	2,3,5	2,3,6	2,4,5	2,4,6	3,4,5	2,3,4,5	2,3,4,6	2,3,5,6	2,3,4,5,6
None	1	2	3	5	7	9	10	12	14	21	23	24	29	30	38	61	62	65	116
2′	4	6	8	16	17	18	19	33	34	41	43	45	48	50	76	86	88	93	142
3′		11	13	20	25	26	27	35	36	55	57	59	67	69	78	106	108	112	160
4′			15	22	28	31	32	37	39	60	63	64	74	75	81	114	115	117	166
2′,3′				40	42	44	46	56	58	82	83	84	97	98	122	129	131	134	173
2′,4′					47	49	51	66	68	85	90	91	99	100	123	137	139	147	181
2′,5′						52	53	70	72	87	92	95	101	103	124	141	144	151	185
2′,6′							54	71	73	89	94	96	102	104	125	143	145	152	186
3′,4′								77	79	105	109	110	118	119	126	156	158	163	190
3′,5′									80	107	111	113	120	121	127	159	161	165	192
2′,3′,4′										128	130	132	138	140	157	170	171	177	195
2′,3′,5′											133	135	146	148	162	172	175	178	198
2′,3′,6′												136	149	150	164	174	176	179	200
2′,4′,5′													153	154	167	180	183	187	203
2′,4′,6′														155	168	182	184	188	204
3′,4′,5′															169	189	191	193	205
2′,3′,4′,5′																194	196	199	206
2′,3′,4′,6′																	197	201	207
2′,3′,5′,6′																		202	208
2′,3′,4′,5′,6′																			209

[a] Nomenclature of the PBBs follows that of polychlorinated biphenyls (PCBs). For several PBB congeners, the indicated structural names do not correspond strictly to the IUPAC rules (primed and unprimed numbers are interchanged). A comprehensive survey of PCB nomenclature, including IUPAC names, is given in Mills *et al.* (2007). This nomenclature includes revised numbering of congeners 107–109.

BZ, Ballschmiter & Zell; IUPAC, International Union of Pure and Applied Chemistry; PBBs, polybrominated biphenyls

individual congeners of PBBs. For example, the PBB congener 3,3′,4,4′,5,5′-hexabromobiphenyl is referred to as PBB-169. The relationship between PBB BZ number and Chemical Abstracts Service (CAS) number is given in Table 1.2.

PBBs can be categorized by degree of bromination, and compounds with the same number of bromines are called homologues. Based on the number of bromine substituents, there are 10 homologous groups of PBBs (monobromobiphenyls to decabromobiphenyls). The mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decabromo congeners can exist in 3, 12, 24, 42, 46, 42, 24, 12, 3, and 1 form(s), respectively (Table 1.3). Homologues with different patterns of substitution are referred to as isomers.

1.1.1 Chemical and physical properties of PBBs

The properties of congeners as reported by earlier investigators may be questionable due to insufficient purification of the congener. More accurate data on physical and chemical properties have been reported recently (Table 1.3; Tittlemier *et al.*, 2002). PBBs are chemically comparable to PCBs, with properties linked to bromine, which is a better leaving group in chemical reactions than chlorine. Pure single PBB compounds are mostly colourless or slightly yellowish, often odourless. The commercial products are typically white, off-white, or beige powdered solids (DiCarlo *et al.*, 1978; Tittlemier *et al.*, 2002). PBBs are characterized by low volatility (Table 1.3), which decreases with increasing bromine number (Farrell, 1980; NTP, 2011). PBBs with three or more bromines are solids (Sundström *et al.*, 1976a; de Kok *et al.*, 1977).

PBBs are nearly insoluble in water, and solubility decreases with increasing bromination. PBBs are soluble in fat (Kay, 1977) and slightly to highly soluble in various organic solvents. Partition ratios between 1-octanol and water (log K_{ow}) increase with the number of bromines (Table 1.3; IARC, 1986). Unlike PCBs, the reactivity of PBBs has not been well studied or documented in the literature. Henry's law constant for the hexabromobiphenyls ranges from 1.4×10^{-8} to 3.9×10^{-8} atm-m^3/mol.

Like PCBs, the chemical stability of PBBs is dependent, in part, on the degree and specific pattern of substitution (bromination). However, PBBs show unusual chemical stability and resistance to breakdown by acids, bases, and reducing and oxidizing agents (Pomerantz *et al.*, 1978). Several of the common isomers photodegrade with reductive debromination upon exposure to ultraviolet light (Sundström *et al.*, 1976a; Kay, 1977; Pomerantz *et al.*, 1978). All highly brominated PBB mixtures are known to debrominate rapidly upon ultraviolet irradiation (DiCarlo *et al.*, 1978). Investigations into the pyrolysis of Firemaster BP-6 in the absence of oxygen (600–900 °C) have shown that bromobenzenes and lower brominated biphenyls are formed, but no polybrominated furans. In contrast, pyrolysis in the presence of oxygen (700–900 °C) yielded some di- to heptabromodibenzofurans (O'Keefe, 1978).

1.1.2 Trade names and composition of commercial mixtures

PBB mixtures have been manufactured mainly as three homologue groups: hexabromobiphenyls, octabromobiphenyls, and decabromobiphenyls (Table 1.4; Neufeld *et al.*, 1977; ATSDR, 2004; NTP, 2011). All commercial PBB mixtures are relatively highly brominated, with bromine contents ranging from about 76% for hexabromobiphenyls to 81–85% for octa- to decabromobiphenyl mixtures (Brinkman & de Kok, 1980). Commercial PBB mixtures were produced primarily by Berk Corporation in the United Kingdom [e.g. Berkflam B-10, Flammex B-10 (decabromobiphenyls)], Chemische Fabrik Kalk [e.g. Bromkal 80–9D (nonabromobiphenyl)] and Ugine Kuhlmann [e.g. Adine 0102

Table 1.2 BZ number, bromine positions, and CAS number for individual PBBs (*n* = 209)

BZ No.	Bromine positions	CAS No.
1	2	2052-07-7
2	3	2113-57-7
3	4	92-66-0
4	2,2′	13029-09-9
5	2,3	115245-06-2
6	2,3′	49602-90-6
7	2,4	53592-10-2
8	2,4′	49602-91-7
9	2,5	57422-77-2
10	2,6	59080-32-9
11	3,3′	16400-51-4
12	3,4	60108-72-7
13	3,4′	57186-90-0
14	3,5	16372-96-6
15	4,4′	92-86-4
16	2,2′,3	
17	2,2′,4	
18	2,2′,5	59080-34-1
19	2,2′,6	
20	2,3,3′	
21	2,3,4	
22	2,3,4′	
23	2,3,5	
24	2,3,6	
25	2,3′,4	
26	2,3′,5	59080-35-2
27	2,3′,6	
28	2,4,4′	6430-90-6
29	2,4,5	115245-07-3
30	2,4,6	59080-33-0
31	2,4′,5	59080-36-3
32	2,4′,6	64258-03-3
33	2′,3,4	
34	2′,3,5	
35	3,3′,4	
36	3,3′,5	
37	3,4,4′	6683-35-8
38	3,4,5	115245-08-4
39	3,4′,5	72416-87-6
40	2,2′,3,3′	
41	2,2′,3,4	
42	2,2′,3,4′	
43	2,2′,3,5	
44	2,2′,3,5′	
45	2,2′,3,6	
46	2,2′,3,6′	
47	2,2′,4,4′	66115-57-9
48	2,2′,4,5	
49	2,2′,4,5′	60044-24-8
50	2,2′,4,6	
51	2,2′,4,6′	97038-95-4
52	2,2′,5,5′	59080-37-4
53	2,2′,5,6′	60044-25-9
54	2,2′,6,6′	97038-96-5
55	2,3,3′,4	97038-99-8
56	2,3,3′,4′	
57	2,3,3′,5	
58	2,3,3′,5′	
59	2,3,3′,6	
60	2,3,4,4′	
61	2,3,4,5	115245-09-5
62	2,3,4,6	115245-10-8
63	2,3,4′,5	
64	2,3,4′,6	
65	2,3,5,6	
66	2,3′,4,4′	84303-45-7
67	2,3′,4,5	
68	2,3′,4,5′	
69	2,3′,4,6	
70	2,3′,4′,5	59080-38-5
71	2,3′,4′,6	
72	2,3′,5,5′	
73	2,3′,5′,6	
74	2,4,4′,5	
75	2,4,4′,6	64258-02-2
76	2′,3,4,5	
77	3,3′,4,4′	77102-82-0
78	3,3′,4,5	
79	3,3′,4,5′	97038-98-7
80	3,3′,5,5′	16400-50-3
81	3,4,4′,5	59589-92-3
82	2,2′,3,3′,4	
83	2,2′,3,3′,5	
84	2,2′,3,3′,6	
85	2,2′,3,4,4′	
86	2,2′,3,4,5	
87	2,2′,3,4,5′	
88	2,2′,3,4,6	77910-04-4
89	2,2′,3,4,6′	
90	2,2′,3,4′,5	
91	2,2′,3,4′,6	
92	2,2′,3,5,5′	

Table 1.2 (continued)

BZ No.	Bromine positions	CAS No.
93	2,2′,3,5,6	
94	2,2′,3,5,6′	
95	2,2′,3,5′,6	88700-05-4
96	2,2′,3,6,6′	
97	2,2′,3′,4,5	
98	2,2′,3′,4,6	
99	2,2′,4,4′,5	81397-99-1
100	2,2′,4,4′,6	97038-97-6
101	2,2′,4,5,5′	67888-96-4
102	2,2′,4,5,6′	80274-92-6
103	2,2′,4,5′,6	59080-39-6
104	2,2′,4,6,6′	97063-75-7
105	2,3,3′,4,4′	
106	2,3,3′,4,5	
107	2,3,3′,4,5′	
108	2,3,3′,4,6	
109	2,3,3′,4′,5	
110	2,3,3′,4′,6	
111	2,3,3′,5,5′	
112	2,3,3′,5,6	
113	2,3,3′,5′,6	
114	2,3,4,4′,5	96551-70-1
115	2,3,4,4′,6	
116	2,3,4,5,6	38421-62-4
117	2,3,4′,5,6	
118	2,3′,4,4′,5	67888-97-5
119	2,3′,4,4′,6	86029-64-3
120	2,3′,4,5,5′	80407-70-1
121	2,3′,4,5′,6	
122	2′,3,3′,4,5	
123	2′,3,4,4′,5	74114-77-5
124	2′,3,4,5,5′	
125	2′,3,4,5,6′	
126	3,3′,4,4′,5	84303-46-8
127	3,3′,4,5,5′	81902-33-2
128	2,2′,3,3′,4,4′	82865-89-2
129	2,2′,3,3′,4,5	
130	2,2′,3,3′,4,5′	82865-90-5
131	2,2′,3,3′,4,6	
132	2,2′3,3′,4,6′	119264-50-5
133	2,2′,3,3′,5,5′	55066-76-7
134	2,2′,3,3′,5,6	
135	2,2′3,3′,5,6′	119264-51-6
136	2,2′,3,3′,6,6′	
137	2,2′,3,4,4′,5	81381-52-4
138	2,2′,3,4,4′,5′	67888-98-6
139	2,2′,3,4,4′,6	
140	2,2′,3,4,4′,6	
141	2,2′,3,4,5,5′	120991-47-1
142	2,2′,3,4,5,6	
143	2,2′,3,4,5,6′	
144	2,2′,3,4,5′,6	119264-52-7
145	2,2′,3,4,6,6′	
146	2,2′,3,4′,5,5′	
147	2,2′,3,4′,5,6	
148	2,2′,3,4′,5,6′	
149	2,2′,3,4′,5′,6	69278-59-7
150	2,2′,3,4′,6,6′	93261-83-7
151	2,2′,3,5,5′,6	119264-53-8
152	2,2′,3,5,6,6′	
153	2,2′,4,4′,5,5′	59080-40-9
154	2,2′,4,4′,5,6′	36402-15-0
155	2,2′,4,4′,6,6′	59261-08-4
156	2,3,3′,4,4′,5	77607-09-1
157	2,3,3′,4,4′,5′	84303-47-9
158	2,3,3′,4,4′,6	
159	2,3,3′,4,5,5′	120991-48-2
160	2,3,3′,4,5,6	
161	2,3,3′,4,5′,6	
162	2,3,3′,4′,5,5′	
163	2,3,3′,4′,5,6	
164	2,3,3′,4′,5′,6	82865-91-6
165	2,3,3′,5,5′,6	
166	2,3,4,4′,5,6	
167	2,3′,4,4′,5,5′	67888-99-7
168	2,3′,4,4′,5′,6	84303-48-0
169	3,3′,4,4′,5,5′	60044-26-0
170	2,2′,3,3′,4,4′,5	69278-60-0
171	2,2′,3,3′,4,4′,6	
172	2,2′,3,3′,4,5,5′	82865-92-7
173	2,2′,3,3′,4,5,6	
174	2,2′,3,3′,4,5,6′	88700-04-3
175	2,2′,3,3′,4,5′,6	
176	2,2′,3,3′,4,6,6′	
177	2,2′,3,3′,4,5′,6′	
178	2,2′,3,3′,5,5′,6	119264-54-9
179	2,2′,3,3′,5,6,6′	
180	2,2′,3,4,4′,5′,6	67733-52-2
181	2,2′,3,4,4′,5,6	
182	2,2′,3,4,4′,5,6′	119264-54-9
183	2,2′,3,4,4′,5′,6	
184	2,2′,3,4,4′,6,6′	119264-56-1

Table 1.2 (continued)

BZ No.	Bromine positions	CAS No.
185	2,2′,3,4,5,5′,6	
186	2,2′,3,4,5,6,6′	119264-57-2
187	2,2′,3,4′,5,5′,6	84303-49-1
188	2,2′,3,4′,5,6,6′	119264-58-3
189	2,3,3′,4,4′,5,5′	88700-06-5
190	2,3,3′,4,4′,5,6	79682-25-0
191	2,3,3′,4,4′,5′,6	
192	2,3,3′,4,5,5′,6	
193	2,3,3′,4′,5,5′,6	
194	2,2′,3,3′,4,4′,5,5′	67889-00-3
195	2,2′,3,3′,4,4′,5,6	
196	2,2′,3,3′,4,4′,5′,6	
197	2,2′,3,3′,4,4′,6,6′	119264-59-4
198	2,2′,3,3′,4,5,5′,6	
199	2,2′,3,3′,4,5,5′,6′	
200	2,2′,3,3′,4,5,6,6′	119264-60-7
201	2,2′,3,3′,4′,5′,6,6′	69887-11-2
202	2,2′,3,3′,5,5′,6,6′	59080-41-0
203	2,2′,3,4,4′,5,5′,6	
204	2,2′,3,4,4′,5,6,6′	119264-61-8
205	2,3,3′,4,4′,5,5′,6	
206	2,2′,3,3′,4,4′,5,5′,6	69278-62-2
207	2,2′,3,3′,4,4′,5,6,6′	119264-62-9
208	2,2′,3,3′,4,5,5′,6,6′	119264-63-0
209	2,2′,3,3′,4,4′,5,5′,6,6′	13654-09-6

BZ, Ballschmiter & Zell; CAS, Chemical Abstracts Service Registry; PBBs, polybrominated biphenyls
From Ballschmiter & Zell (1980), Ballschmiter *et al.* (1992)

(decabromobiphenyl)] in Germany, and Michigan Chemical Corporation, White Chemical Corporation, and Hexcel Corporation in the USA [e.g. Firemaster BP-6 (CAS No. 59536-65-1) and FF-1 (CAS No. 67774-32-7)].

The exact composition of the mixtures varies between batches (see Section 1.3; Table 1.5) and also within each batch, according to sampling (see Section 1.2). The main constituents of Firemaster are hexabromobiphenyl (63–84%) and heptabromobiphenyl (12–25%), together with lesser brominated [pentabromobiphenyl (1–11%) and tetrabromobiphenyl (0–5%)] congeners (Sundström *et al.*, 1976b; DiCarlo *et al.*, 1978; Hass *et al.*, 1978; Robertson *et al.*, 1984a) due to incomplete bromination reactions (IPCS, 1994).

At least four ^{13}C-labelled PBB congeners are available commercially.

1.1.3 Contaminants and impurities of commercial mixtures of PBBs

Mixed polybromochlorobiphenyls (PXBs), e.g. monochloropentabromobiphenyl (CAS No. 88703-30-4), have been observed as minor contaminants in Firemaster (Tondeur *et al.*, 1984). Such compounds probably result from contamination of commercial bromine by chlorine (Domino & Domino, 1980). Contaminants of the initial biphenyl feedstock may ultimately appear in commercial mixtures of PBBs. Described impurities include toluene, naphthalene, methylene biphenyl (fluorene) and various methyl biphenyls (Neufeld *et al.*, 1977). It is assumed that naphthalene for instance, present as an impurity in industrial-grade biphenyl, is brominated during production, and that the presence of numerous isomers and congeners of polybrominated naphthalenes in the final product is possible (Robertson *et al.*, 1984a). Polybrominated benzenes and a possible methylbrominated furan have also been reported to occur in Firemaster(R) (Brinkman & de Kok, 1980). Polybromodibenzo-*p*-dioxins and polybromodibenzofurans were not detected above 0.5 mg/kg in the polar fraction of Firemaster FF-1 (Hass *et al.*, 1978). In another study, O'Keefe (1978) showed that polybrominated dibenzofurans were formed during pyrolysis of Firemaster FF-1. A sample of Adine 0102 (decabromobiphenyl) contained monobromobenzodifurans at 1 mg/kg and polybromodibenzodioxins and polybromodibenzofurans at below 0.01 mg/kg (IPCS, 1994). Although PBBs are relatively stable, highly brominated congeners are susceptible to photolytic debromination when they are exposed to ultraviolet light (see Section 1.1.1).

Table 1.3 Physical and chemical properties of homologue groups of PBBs

Homologue group	CAS No.	Formula	No. of isomers	BZ No.	Relative molecular mass	Melting point (°C)	Solubility (μg/L)	Volatility (Pa at 25 °C)[a] (calculated)[b]	Log K_{ow}[a]
Monobromobiphenyls	26264-10-8	$C_{12}H_9Br_1$	3	1–3	232.9				4.6 (PBB-1)
Dibromobiphenyls	27479-65-8	$C_{12}H_8Br_2$	12	4–15	311.8				
Tribromobiphenyls	51202-79-0	$C_{12}H_7Br_3$	24	16–39	390.7				
Tetrabromobiphenyls	40088-45-7	$C_{12}H_6Br_4$	42	40–81	469.6			5.0×10^{-4}	6.5 (PBB-52)
Pentabromobiphenyls	56307-79-0	$C_{12}H_5Br_5$	46	82–127	548.5			2.7×10^{-5}	7.2 (PBB-101)
Hexabromobiphenyls	36355-01-8	$C_{12}H_4Br_6$	42	128–169	627.4	72	11–3[b]	1.4×10^{-6}	8.0 (PBB-153)
Heptabromobiphenyls	35194-78-6	$C_{12}H_3Br_7$	24	170–193	706.3			1.1×10^{-7}	8.3 (PBB-180)
Octabromobiphenyls	27858-07-7	$C_{12}H_2Br_8$	12	194–205	785.2	200–255	20–30	8.7×10^{-9}	8.7 (PBB-194)
Nonabromobiphenyls	27753-52-2	$C_{12}H_1Br_9$	3	206–208	864.1			1.7×10^{-9}	9.1 (PBB-206)
Decabromobiphenyls	13654-09-6	$C_{12}Br_{10}$	1	209	943.0	380–386	Insoluble	3.2×10^{-10}	9.4 (PBB-209)

[a] Values are examples of one congener in the homologue group.

[b] Calculated using Advanced Chemistry Developement (ACD/Labs) Software VII.02 (©1994–2010 ACD/Labs).

[c] Tittlemier *et al.* (2002)

BZ, Ballschmiter & Zell; PBBs, polybrominated biphenyls

From IARC (1978), EFSA (2010)

Table 1.4 Trade names of commercial PBB mixtures

Main PBB congeners	Trade name
Hexabromobiphenyls	Firemaster FF-1
	Firemaster BP-6
	"Hexabromobiphenyl"
Octabromobiphenyls	BB-8
	Bromkal 80
	Bromkal 80–9D
	Octabromobiphenyl FR 250 13A
	Technical octabromobiphenyl
Decabromobiphenyls	Adine 0102
	Berkflam B-10
	Flammex B-10
	HFO 101
	Technical decabromobiphenyl

PBB, polybrominated biphenyl
From IPCS (1994)

1.2 Analysis

Given that the physical and chemical characteristics of PBBs are similar to those of PCBs, sampling techniques for PBBs are essentially identical to those described for PCBs. However, a considerably smaller body of scientific literature is available on PBBs than on PCBs, and not all environmental matrices have been studied.

As with all brominated flame retardants, samples should not be exposed to sunlight, since PBBs are unstable when exposed to ultraviolet radiation (Brinkman & de Kok, 1980).

1.2.1 Environmental and food samples

PBBs were analysed together with polychlorinated dibenzodioxins/polychlorinated dibenzofurans (PCDD/PCDFs), PCBs and polybrominated diphenyl ethers (PBDEs) in the same air samples (Wang *et al.*, 2010a). Particles and gaseous phase were collected on glass-fibre filters and polyurethane foam, respectively, as described for PCBs. After Soxhlet extraction with toluene, extracts were treated with acid and purified on acid silica. In a second clean-up step on alumina, several fractions were obtained, including fractions with non-polar PBBs/PCBs and polar PBBs/PCBs.

Most studies combine the analysis of PBBs with that of PBDEs, for example, for soil (Wang *et al.*, 2009) or sediment samples (de Boer *et al.*, 2003). After freeze-drying and sieving, the samples were mixed with copper for sulfur removal, as described for analysis of PCBs in soils and sediments, Soxhlet extracted, and cleaned up on silica-gel columns. Besides Soxhlet extraction, pressurized liquid extraction has also been used for sediment analysis (Zhao *et al.*, 2010). Clean-up processes included multilayer columns of acid, neutral and basic silica gel, as well as gel-permeation chromatography and subsequent treatment with sulfuric acid (de Boer *et al.*, 2003; Zhao *et al.*, 2010).

Water samples were analysed in terms of influent and effluent samples of waste-water treatment plants (de Boer *et al.*, 2003). The samples were filtered or centrifuged to separate suspended particulate matter from the water phase, and then treated as for sediment samples, i.e. Soxhlet extraction of the particulate phase, gel-permeation chromatography, acid treatment and clean-up with silica gel.

Several studies have analysed fish samples, with a focus on the most biaccumulative congener PBB-153. The samples were dried, either by freeze-drying (Gieroń *et al.*, 2010) or with sodium sulfate (de Boer *et al.*, 2003), and extracted using a Soxhlet apparatus (de Boer *et al.*, 2003; Zhu & Hites, 2004) or direct extraction with dichloromethane in an extraction column (Luross *et al.*, 2002). Lipids were removed by acid treatment, using acid silica gel (Gieroń *et al.*, 2010) or direct treatment with sulfuric acid (de Boer *et al.*, 2003). Further clean-up and fractionation techniques included gel-permeation chromatography, column clean-up with alumina or with neutral/basic silica and the dialysis through semi-permeable membrane devices (Gieroń *et al.*, 2010).

Table 1.5 Composition of commercial PBB mixtures

Composition	Commercial mixture (range of % bromination)			
	Hexabromobiphenyls	Octabromobiphenyls[a]		Decabromobiphenyls
Tetrabromobiphenyls	2–5			
Pentabromobiphenyls	1–11			
Hexabromobiphenyls	63–84	0	1–2	0–4
Heptabromobiphenyls	12–25	1–7	23–27	0–4
Octabromobiphenyls	0–2	25–57	46–72	0–7
Nonabromobiphenyls		0–28	34–65	2–11
Decabromobiphenyls		2–9	0–1	71–97

[a] The Working Group noted that the "octabromobiphenyls" include two classes of mixtures with different ranges of composition. In IPCS (1994), they are called "octanonabromobiphenyls."
PBB, polybrominated biphenyl
From de Kok *et al.* (1977), IPCS (1994)

Gieroń *et al.* (2010) also analysed other food products using this method; pure lipid samples (butter, pork adipose tissue) were melted before further processing. Analytical methods for PBBs in food were summarized by EFSA (2010), describing solvent extraction, lipid removal and additional clean-up by column chromatography.

1.2.2 Biological samples

Several studies have been conducted on the Michigan cohort, which was established in 1976 following the accidental contamination of cattle feed with PBBs and subsequent exposure of local residents (see Section 1.4). Human serum samples were analysed at enrolment in the cohort (1976–1978) and in the follow-up studies until 1993 (Givens *et al.*, 2007). After protein denaturation with methanol, PBBs were extracted with hexane:diethyl ether (1:1), and extracts were cleaned on Florisil (Burse *et al.*, 1980; Needham *et al.*, 1981). More recent blood analyses did not deviate much from these procedures, but applied a higher degree of automatization (Frederiksen *et al.*, 2010). The first step was generally protein denaturation, often using formic acid. Solid-phase extraction was a common extraction technique, followed by lipid removal using H_2SO_4 (Wang *et al.*, 2010b) or clean-up on acid and neutral silica (Sjödin *et al.*, 2004a) and/or Florisil (Sandanger *et al.*, 2007; Wang *et al.*, 2010b). Blood analyses have generally focused on PBB-153 as the congener with the most pronounced bioaccumulation.

For the analysis of human milk, EFSA (2010) described solvent extraction and solid-phase extraction, followed by the same clean-up method as for food samples. Adipose tissue has also been analysed for PBBs, in combination with PBDEs and PCBs (Fernandez *et al.*, 2007; Miceli *et al.*, 1985). The samples were Soxhlet-extracted using toluene or hexane:acetone. Lipids were removed on acid silica gel. Further clean-up included neutral and basic silica gel and a fractionation into different compound groups. Target PBBs and PBDEs were separated from PCDD/PCDFs on an activated carbon column and further cleaned up on alumina (Fernandez *et al.*, 2007), while separation of PCBs from the brominated compounds was achieved by different solvents eluting the compounds from the silica-gel column (Zhao *et al.*, 2009).

1.2.3 Instrumental analysis

As described for PCBs, the instrumental analysis of PBBs is basically independent of the original matrix, although selectivity and

sensitivity should be considered. It also is worth noting that PBBs often are analysed in conjunction with other substances, making multicompound methods desirable. For example, studies including the determination of dioxins and furans or other coplanar molecules besides PBBs have used high-resolution gas chromatography (HRGC) in combination with high-resolution mass spectrometry (HRMS) (Wang *et al.*, 2010a), which is a highly selective and very sensitive technique. Owing to these advantages, HRGC–HRMS has also been applied in analyses of environmental and biological samples that have combined determination of PBDEs and PBBs (Luross *et al.*, 2002).

Gas chromatography–mass spectrometry (GC–MS) with electron-capture negative ionization (ECNI) is a common method in the analysis of PBBs, providing high sensitivity (de Boer, 1999). However, PBB-153, the predominant congener in biological matrices, co-elutes with the PBDE BDE-154 on several GC columns. As both congeners are detected by the mass fragments m/z = 79 and m/z = 81, chromatographic separation must be achieved to avoid miscalculations, for example on a 60 m capillary column (Zhu & Hites, 2004). On the other hand, a shorter column is advisable for the determination of PBB-209, which is not stable at elevated temperatures (de Boer, 1999; Zhao *et al.*, 2009). As the GC–MS (ECNI) method relies on the detection of the bromide ion, the use of ^{13}C-labelled standards is excluded.

GC–MS with electron impact (EI) ionization has also been used for environmental and biological samples (Zhao *et al.*, 2009; Gieroń *et al.*, 2010), allowing detection of molecular ions and specific fragments. However, this technique is described as being 10 times less sensitive than GC–MS (ECNI) and GC with electron capture detection (ECD) (de Boer, 1999). GC–ECD was generally used in the early studies (Burse *et al.*, 1980), and although still applied in environmental and biological analyses (Wang *et al.*, 2009; Wang *et al.*, 2010b), is increasingly replaced by GC–MS techniques.

1.2.4 PXBs

Only few studies have analysed mixed chlorinated/brominated biphenyls, as recently reviewed by Falandysz *et al.* (2012). Eight native congeners and their ^{13}C-labelled analogues were commercially available for this analysis. Other studies, which rely on custom-made analytical standards, analysed fewer congeners (Ohta *et al.*, 2008a).

PXBs were generally analysed together with other compounds, primarily PCDD/PCDFs, by extending existing methods. Additional fractionation steps on carbon columns were included to isolate the PXB congeners. They were analysed by HRGC–HRMS using isotope dilution quantification, although not all studies used matching native and labelled congeners (Falandysz *et al.*, 2012).

PXBs have been analysed in food (Fernandes *et al.*, 2011), fish (Ohta *et al.*, 2008a) and human milk (Gómara *et al.*, 2011), focusing on five to eight congeners. Fernandes *et al.* (2011) described an extensive sample clean-up involving acid and basic silica gel and several carbon columns, to isolate non-*ortho* and mono-*ortho* PXBs, respectively.

1.3 Production and uses

Production of PBBs generally involves the reaction of biphenyl with bromine and chlorine in a solvent with aluminum chloride as a catalyst (Neufeld *et al.*, 1977). PBBs are also formed as impurities during the production of other brominated compounds. For example, PBBs are formed during the production of decabromodiphenyl oxide because of the presence of diphenyl as an impurity in the starting material, diphenyl oxide (Neufeld *et al.*, 1977). PBBs are also present as impurities in PBDEs (Hanari *et al.*, 2006).

Commercial PBB mixtures were manufactured primarily as flame retardants. In the USA and Europe, PBB mixtures were produced and sold commercially as products with a specific bromine content. Although these commercial products are generally referred to as "hexabromobiphenyl," "octabromobiphenyl," and "decabromobiphenyl," these are misnomers, since each commercial product contained numerous congeners with different numbers of bromine substitutions (see Section 1.1.2). The composition of commercial products varied substantially across lots and producers (Table 1.5), particularly for octabromobiphenyls, many of which may actually have consisted primarily of nonabromobiphenyls.

PBBs were produced by three companies in the USA during the 1970s only. One company in Michigan produced hexabromobiphenyl, and two companies in New Jersey produced octabromobiphenyl and decabromobiphenyl. Total production in the USA was estimated at 13 million pounds [5896 tonnes], 88% of which was hexabromobiphenyl (Table 1.6). Production of hexabromobiphenyl in Michigan was halted in 1974 subsequent to the contamination of animal feed (see Section 1.4), and production of octabromobiphenyl and decabromobiphenyl was discontinued a few years later (Neufeld *et al.*, 1977). In the United Kingdom, PBBs were produced until 1977; in Germany, until the mid 1980s; and in France, until 2000, with only decabromobiphenyl being produced in the later years (EFSA, 2010). No information was available on production volumes in Europe or elsewhere.

In addition to these commercial producers, a few speciality chemical companies produced PBBs with lower bromine content, mostly monobromobiphenyls and dibromobiphenyls, in small batches of 0.1–1 kg, to be used in functional fluids (Neufeld *et al.*, 1977).

The major uses of PBBs were in acrylonitrile-butadiene-styrene (ABS) plastics (used, for example, for housing television sets and other electronic machines), in coatings and lacquers, and in polyurethane foam. Based on a PBB content of 10%, an estimated 118 million pounds [53.5 tonnes] of PBB-containing ABS plastic could have been made during 1971–1975, which would be about 5% of the total production of ABS plastics during those years (Neufeld *et al.*, 1977). In these uses, PBB flakes were physically blended into the product, not chemically incorporated into a polymer (Neufeld *et al.*, 1977). This raises the concern that they could volatilize or leach out of the product (ATSDR, 2004).

Recently, PBBs were detected in electronic waste in cable coatings, stuffing powder for electronic components, and circuit boards, suggesting uses in such equipment. PBBs in these items consisted mostly of mono-, di-, or tribromobiphenyls (Zhao *et al.*, 2008). [The Working Group noted that this is not consistent with hexa-, octa-, and decabromobiphenyl being the only commercial mixtures with large-scale production and use. This suggests that PBBs of predominantly low bromine content may have been used in electronic equipment in China, which was previously unknown. The Working Group noted the small sample size.]

PXBs can be formed when chlorine and bromine are present during the combustion of PCBs or PBBs. PXBs are also contaminants of commercial PCB mixtures, resulting from the presence of bromine gas as a trace contaminant of the chlorine gas used in the production of PCBs. Dioxin-like PXBs can be formed during pyrolysis or photolysis of PBDEs. PXBs are not known to be produced intentionally (Falandysz *et al.*, 2012).

1.4 Environmental occurrence and human exposure

PBBs can enter the general environment from several sources: loss during production of PBBs, loss during manufacture of products containing PBBs, disposal and reprocessing

Table 1.6 Production volumes of commercial PBB mixtures in the USA

Year	Hexabromobiphenyls	Octa- and decabromobiphenyls	Total (tonnes)
1970	0.95	14.0	24
1971	84	14.0	98
1972	1007	14.5	1022
1973	1764	162	1927
1974	2214	48.0	2263
1975	0	77	77
1976	0	365	365
1977	0	> 0	> 0
Total (%)	5079 (88%)	> 7046 (12%)	> 5775 (100%)

PBB, polybrominated biphenyl
Adapted from DiCarlo *et al.* (1978)

of products containing PBBs, and accidental releases. Products from the 1970s that contained PBBs have generally reached the end of their useful life and would have been recycled, disposed of in landfills, or incinerated.

It was estimated that the production of 805 000 pounds [365 tonnes] of decabromobiphenyl in the USA in 1976 resulted in 5% loss to the environment: 900 pounds [408 kg] to air, 0.0037 pounds [1.7 g] to wastewater, and 40 250 pounds [18.3 tonnes] to landfills as solid waste (Neufeld *et al.*, 1977). [The wastewater calculation for decabromobiphenyl considered only the solubility of PBBs in water, which is low, and not the likelihood that solid PBB particles could also be discharged in wastewater.] Similar figures were not located on losses from production of hexabromobiphenyl, but discharges in 1974 from the plant in Saint Louis, Michigan, USA, were estimated at 0.11 kg per day (Archer *et al.*, 1979). [The hexabromobiphenyl mixture has a higher vapour pressure and a higher fraction of congeners with low bromine content, which generally would be more volatile.]

Contamination with PBBs has been high in Michigan, owing to accidental widespread contamination of farms, foods, and residents. In early 1973, several bags of the hexabromobiphenyl mixture "Firemaster" were mistaken for "NutriMaster," an animal feed supplement containing magnesium oxide. Both products were manufactured at the same plant. A shortage of preprinted paper bags at the plant led to 10–20 50-pound [22.7 kg] bags of Firemaster being packed in NutriMaster paper bags and sent to animal-feeding operations (Michigan Department of Community Health, 2011).

PBB concentrations in the contaminated feed were estimated to be between 4000 and 13 500 ppm [mg/kg]. In addition, there were four routes of indirect contamination with PBBs (Kay, 1977):

- Processing or mixing of clean feed in contaminated grain elevators (chicken feed became contaminated in this way).
- Incorporation of material from contaminated animals that died (and were sent to a rendering plant) into animal feed.
- Processing of contaminated milk into milk powder for feeding young animals.
- Swapping of feed by farms and feed mills.

The error was not discovered until April 1974, by which time the PBBs had entered the food chain through contaminated milk, eggs and other dairy products, contaminated beef products, and contaminated swine, sheep, and chickens. More than 500 Michigan farms were quarantined and 30 000 cattle, 1500 sheep, and 1.5 million chickens were destroyed. Inventories of 800 tons [725 tonnes] of animal feed, 18 000

pounds [8.1 tonnes] of cheese, 2500 pounds [1.1 tonnes] of butter, 5 million eggs, and 34 000 pounds [15.4 tonnes] of dried milk products were also destroyed (Michigan Department of Community Health, 2011).

PBBs have generally been replaced by PBDEs. PBBs, however, are present as impurities in PBDEs. On the basis of PBDE production and use in 2001, it was estimated that potential global annual emissions of PBBs would be 40 kg (Hanari *et al.*, 2006). [The Working Group noted that the Michigan incident involved 500–1000 pounds [225–450 kg] of PBBs.] There were few reports of recent concentrations of PBBs in environmental media; most investigations of brominated compounds have focused on PBDEs and newer brominated alternatives for use as flame retardants.

1.4.1 Environmental fate

In the environment, PBBs occur as mixtures of congeners whose compositions differ from that of the commercial products. This is because after release into the environment, composition changes over time because of partitioning, chemical transformation, and bioaccumulation. PBB congeners are highly persistent in the environment and in biological tissues. Air and water are the transport media.

Primarily hydrophobic, PBBs adsorb strongly to soils and sediments. Hydrophobic adsorption generally increases with the bromine content of the PBB congener and the organic content of the soil or sediment. In water, PBBs with high bromine content are less soluble and more likely to attach strongly to sediment. PBB congeners with low bromine content are more likely to be soluble in water. In air, PBB congeners are generally not very volatile, and are less volatile than the corresponding PCB congeners (Pijnenburg *et al.*, 1995).

PBBs are lipophilic and can be dissolved in solvents. Liquid solvents that may be present in landfills or contaminated sites are capable of solubilizing PBBs and carrying them to distant locations (ATSDR, 2011). PBBs are 200 times more soluble in landfill leachate than in distilled water, and more soluble in creek water than in purified water. These results are correlated with the levels of dissolved organic compounds (Lewis, 1981).

PBBs degrade slowly in the environment. In 1988, sediments from Pine River, Michigan, contained 10–12% PBB congeners that are not found in Firemaster, consistent with bromines being selectively removed from *meta* and *para* positions. Microorganisms are capable of debrominating PBB congeners, although this process can be inhibited by organic co-contaminants, petroleum products, and heavy metals. Ultraviolet light can degrade PBB congeners, especially at *ortho* positions (Pijnenburg *et al.*, 1995).

Bioconcentration and bioaccumulation are important processes for PBBs in water. Bioconcentration from water is more pronounced for PBBs with low bromine content. The pattern for bioaccumulation from food is more complex (Pijnenburg *et al.*, 1995).

1.4.2 Natural occurrence

PBBs and PXBs are not known to occur in nature.

1.4.3 Air and dust

In the past, PBBs were released into the air during manufacture. Air emissions through vents were reported to be $2–3 \times 10^{-6}$ mg/L (Neufeld *et al.*, 1977; Vorkamp *et al.*, 2005; Wang *et al.*, 2010a). PBBs were detected at a concentration of 6×10^{-11} mg/L in air samples near a PBB-manufacturing plant, although the same concentration was measured downwind and crosswind from the plant (DiCarlo *et al.*, 1978).

Another potential source of PBBs in air is from incineration of products containing PBBs. Pyrolysis of commercial hexabromobiphenyl

produces small amounts of lesser brominated biphenyls (Thoma & Hutzinger, 1987).

Near a municipal solid waste incinerator in Taiwan, China, PBB concentrations in air were reported as 149–556 fg.N/m^3 (Wang *et al.*, 2010a).

PBB-153 was not detected in house dust in Bavaria, Germany, with a limit of detection of 10 ng/g (Kopp *et al.*, 2012).

No other information was available on recent concentrations of PBBs in outdoor or indoor air.

PXBs have been found in exhaust gas from waste incinerators and in marine sediments in Japan (Ohta *et al.*, 2009).

1.4.4 Water, sediment, and sewage sludge

No data were available on recent concentrations of PBBs in surface water, groundwater, or sediment.

In the past, PBBs were released into water during manufacture. PBBs have been found in a variety of surface waters, groundwater, and sediments. This is most probably due to solid PBB particles being carried along with the water, as PBBs are rather insoluble in water. As might be expected, concentrations in river water and sediments tend to decrease with distance downstream from the source (Table 1.7). Although most sampling has occurred in and around PBB-production plants, PBBs have also been detected in wastewater from the production of decabromodiphenyl oxide (in which PBBs are a byproduct) and in effluents and sludge from a municipal wastewater-treatment plant (Neufeld *et al.*, 1977; Daso *et al.*, 2012).

Wastewater discharges from the Michigan Chemical Corporation plant provide an instructive example. In 1972, PBB particles were measured in wastewater from the plant at concentrations up to 98–503 µg/L. In 1974, after actions to reduce the discharge of PBB particles, concentrations of up to 100 µg/L persisted. In 1975, after PBB production was halted, concentrations as high as 150 µg/L were measured irregularly. In 1977, after removal of contaminated soil from bagging and loading areas of the plant, concentrations fell to below 1 µg/L (Hesse & Powers, 1978).

In 1999, PBBs were not found in suspended particulate matter, sediments, sewage treatment plant influents and effluents, fish, and mussels in the Netherlands (limit of detection, 0.1–1 µg/kg dry weight; 1–10 µg/kg for PBB-209) (de Boer *et al.*, 2003).

1.4.5 Soil

PBBs are found at nine sites on the United States Environmental Protection Agency's National Priorities List ("Superfund" sites), four of them in Michigan (ATSDR, 2011), including the site of the Michigan Chemical Corporation plant. In 1975, soil from bagging and loading areas of the Michigan Chemical Corporation plant contained PBBs at 3500 and 2500 mg/kg, respectively (Hesse & Powers, 1978) and soil near the two PBB-production plants in New Jersey, USA, contained PBBs at 40–3100 and 750–2800 µg/kg, respectively (DiCarlo *et al.*, 1978). Soil samples from 28 fields that received manure from Michigan's most highly contaminated dairy herds had the following distribution of PBB concentrations: below detection limit of 0.1 µg/kg, two fields; 0.1–0.9 µg/kg, six fields; 1–9 µg/kg, nine fields; 10–99 µg/kg, five fields; 100–371 (maximum) µg/kg, six fields. PBBs were not detected in two control farm fields. PBBs also were below the detection limit of 0.3 µg/kg in corn, alfalfa, and sudangrass that was being grown in the contaminated fields (Jacobs *et al.*, 1978).

Soil samples near facilities that processed PBBs in California and West Virginia, USA, contained PBBs at up to 36 000 and 12 µg/kg, respectively (Zweidinger & Pellizzari, 1980).

In 2007, PBB concentrations were measured in soil collected from four villages in China where electronic-waste disassembly sites were located. The median PBB concentration was

Table 1.7 Concentrations of PBBs in various environmental media

Medium	Site	PBB concentration	Reference
Wastewater	Original discharge from Michigan PBB plant	98–503 µg/L	Hesse & Powers (1978)
	After some action to reduce discharges	≤ 100 µg/L	Hesse & Powers (1978)
	After PBB production stopped	Erratic, ≤ 150 µg/L	Hesse & Powers (1978)
	After soil cleanup at plant	< 1 µg/L	Hesse & Powers (1978)
Wastewater	Decabromodiphenyl oxide production	< 0.1–10 µg/L	Neufeld *et al.* (1977)
Storm sewer water	Near New Jersey PBB plant	92 µg/L	DiCarlo et al. (1978)
Swamp water	Runoff from New Jersey PBB plant	135 µg/L	DiCarlo et al. (1978)
River water	Near effluent discharge of Michigan PBB plant	13 µg/L	Archer *et al.* (1979)
	13 km downstream	0.01 µg/L	Archer et al. (1979)
	12 miles downstream of Michigan PBB plant	0.01–0.07 µg/L	Hesse & Powers (1978)
	25–29 miles downstream	ND (< 0.1 µg/L)	Hesse & Powers (1978)
Sediment	Near New Jersey PBB plant	100 mg/kg	Archer *et al.* (1979)
	At Michigan PBB plant	77 mg/kg	Hesse & Powers (1978)
	Just downstream of plant	6.2 mg/kg	Hesse & Powers (1978)
	29 miles downstream	0.1 mg/kg	Hesse & Powers (1978)
Groundwater	Near landfill from Michigan PBB plant	0.1–0.2 µg/L	DiCarlo *et al.* (1978)
Drainage ditch, catch basin	Near landfill from Michigan PBB plant	1.2 mg/kg	DiCarlo et al. (1978)
Effluent	Wastewater treatment plant in South Africa	< 18.4 ng/L	Daso *et al.* (2012)
Sewage sludge	Wastewater treatment plant in South Africa	< 9.97 ng/g	Daso et al. (2012)

ND, not detected; PBBs, polybrominated biphenyls

22 µg/kg (range, 18–58 µg/kg; n = 6) compared with 11 µg/kg (range, 8–19 µg/kg; n = 3) in a remote village at a distance of 30 km where there were no electronic-waste operations. Mono-, di-, and tribromobiphenyls predominated, with PBB-2 being the single most abundant congener (Zhao *et al.*, 2008).

Soils from urban and rural sites in the United Kingdom contained dioxin-like PXBs, with concentrations an order of magnitude greater in urban soil than in rural soil. Concentrations of four mono-*ortho* PXBs were 0.90, 0.49, and 0.17 ng/kg in urban soil, and 0.050, 0.025, and 0.024 ng/kg in rural soil (Fernandes *et al.*, 2011).

1.4.6 Bioaccumulation in wildlife and plants

Field studies in several species show that PBBs are taken up by wildlife. Near the Michigan Chemical Corporation plant, PBBs have contaminated fish in the Pine River downstream from the plant. PBBs were detected in 25 out of 27 composite samples, where each sample represented one out of seven fish species taken at one out of four sampling stations. The highest concentration was 1.33 mg/kg in skinless carp fillets. PBBs were not detected in fish samples collected upstream of the plant above a dam that prevents upstream fish movement, and PBBs were not detected in fish samples from a nearby river. PBBs were detected in the majority of wild ducks collected within 2 miles of the plant. Near a PBB-production plant in New Jersey, a turtle was found to contain hexabromobiphenyl at 20 µg/kg. More recently, PBB congeners, predominantly PBB-153, were detected in lake trout from the Great Lakes (DiCarlo *et al.*, 1978; Hesse & Powers, 1978; Luross *et al.*, 2002).

The strong bioaccumulation potential of PBBs was demonstrated in caged fish in the Pine River near the Michigan Chemical Corporation plant. After 2 weeks of exposure, concentrations in caged fathead minnows were up to 10 000 times those in the surrounding river water. No

PBBs were detected in fish sampled at a control station 3 miles upstream of the plant (Hesse & Powers, 1978).

PBBs have been measured in a variety of marine species. These positive measurements, made at sites far from industrial sources of PBBs, indicate that PBBs can be transported great distances. The detection of PBBs in sperm whales indicate that these compounds have reached deep ocean waters, as sperm whales are not usually found in shallow seas (Jansson *et al.*, 1987, 1993; de Boer *et al.*, 1998). [It is noteworthy that whenever a species has been sampled in the same area in different years, the levels have increased.]

PBB-153 was detected in the eggs of six species of wild aquatic birds, one species of wild terrestrial bird, and two species of captive birds in China. Levels ranged from non-detectable to 0.7 ng/g lipid weight (Vorkamp *et al.*, 2005; Gao *et al.*, 2009).

PBBs were taken up by root vegetables grown in soil artificially contaminated with PBBs. Most of the residue was on the vegetable surface and could be removed by dipping in acetone. Uptake was higher by plants grown in a sandy soil than in a clay soil with higher organic content. This is consistent with the tendency of PBBs to adsorb to soils with high organic content. No PBBs were detected in orchard grass or in carrot tops (Jacobs *et al.*, 1976; Chou *et al.*, 1978; DiCarlo *et al.*, 1978).

1.4.7 Food and estimated dietary intake

Soon after the Michigan incident was discovered, sampling on contaminated farms revealed BBP concentrations as high as 595 mg/L in milk, 4600 mg/kg in poultry tissue, 60 mg/kg in eggs, and 2700 mg/kg in cattle tissue (Kay, 1977).

In milk from contaminated dairy herds, the concentration of PBBs was estimated to have reached 6000 mg/L after 15 days exposure, declining to 1800 mg/L 15 days after exposure ceased, and to 160 mg/L after another 230 days (Fries *et al.*, 1978).

Based on monitoring of PBBs in food and a call for data, the European Food Safety Authority (EFSA) evaluated results on 794 food samples collected during 2003–2009 from Belgium, Estonia, France, Ireland, Spain, and the United Kingdom (5643 analytical results covering 16 PBB congeners). Due to the large number of non-detects for individual congeners in individual samples, EFSA focused the analysis on seven congeners: those with less than 80% non-detects, plus the three coplanar PBBs PBB-77, PBB-126, and PBB-169. The EFSA analysis provided the ranges of these PBB congeners in four food categories (Table 1.8; EFSA, 2010).

Based on recent estimates of mean and high dietary exposure to the different food categories, EFSA calculated average and high-end intakes of five PBB congeners from food. For children aged 1–3 years, the principal source was milk, with an intake of 32 or 64 pg/kg bw per day for average or high-end consumers, respectively. For children aged 3–6 years, the principal source was fish and seafood, with an intake of 15 or 66 pg/kg bw per day for average or high-end consumers, respectively. For adults, the principal source was fish and seafood, with an intake of 8 or 40 pg/kg bw per day, respectively. Food supplements would add another 39 pg/kg bw per day (Table 1.9; EFSA, 2010). [Including only five congeners in the analysis could lead to a substantial underestimate of intake, especially if a potent congener were omitted because it is not widely distributed across a broad food category.]

PXBs were detected in nine species of domestic or imported fish and one species of marine mammal from food markets in Japan. Toxic equivalency (TEQ), calculated as a weighted sum of the concentrations of five non-*ortho* congeners, ranged from 0.09 to 1.3 pg/g wet weight. When compared with TEQs calculated as a weighted sum of the concentrations of 12 PCB congeners, the predicted toxicity levels attributable to PXBs or PCBs were generally within one order of magnitude. The authors concluded that

Table 1.8 Mean concentration (pg/g wet weight) of seven PBB congeners in foods in Europe

PBB congener	Meat, meat products		Milk, dairy products		Fish, seafood		Food for infants, small children	
	LB	UB	LB	UB	LB	UB	LB	UB
PBB-49	–	–	–	–	1.32	1.52	–	–
PBB-52	0.06	0.39	0.01	0.58	4.19	4.31	–	–
PBB-101	0.06	0.39	0.01	0.58	1.55	1.86	–	–
PBB-153	–	–	–	–	0.81	18.9	0	7.64
PBB-77[a]	0.0002	0.0055	0	0.0051	0.0168	0.0226	–	–
PBB-126[a]	0.0045	0.0107	0	0.004	0.0005	0.0087	–	–
PBB-169[a]	0	0.0077	0	0.0071	0	0.0088	–	–

[a] Original data on non-*ortho* PBBs were reported with considerably lower LOQs. Therefore the number of digits after the decimal point has been extended to four in this table, for descriptive reasons.
LB, lower bound; PBB, polybrominated biphenyl; UB, upper bound
From EFSA (2010)

dioxin-like PXBs cannot be considered a negligible contributor to human health risks. The authors also remarked that the lack of availability of analytical standards made it impossible to identify and quantify most PXB congeners (Ohta *et al.*, 2008b). PXBs have been detected in seal blubber in ng/g lipid concentrations (Falandysz *et al.*, 2012).

Non-*ortho* and mono-*ortho* PXBs have been detected in several foods in the United Kingdom, including soft cheese, cow milk, duck eggs, lamb, liver, vegetables, river fish, and marine fish (Fernandes *et al.*, 2011).

1.4.8 Exposure of the general population

In 1976–1977, venous blood samples were drawn from several groups of Michigan residents and analysed for PBBs with a limit of detection of 1 µg/L. They showed a wide range of concentrations within each group of residents, and distinctly higher mean concentrations for three groups: chemical workers engaged in PBB production and their families, residents of quarantined farms, and direct recipients of products from such farms (Table 1.10; Landrigan *et al.*, 1979). [The Working Group noted that the inclusion of family members of chemical workers was likely to have reduced the reported levels for the chemical workers: while Table 1.10 (Landrigan *et al.*, 1979) shows a range of non-detect to 1240 µg/L for 216 chemical workers and their family members, Table 1.11 (Anderson *et al.*, 1978a) shows that none of the 55 chemical workers had a level less than 1.1 µg/L.]

In another report, the distribution of serum PBB concentrations in Michigan chemical workers was shown to be distinctly higher than that of farm residents (Table 1.11; Anderson *et al.*, 1978a).

In the same study, maternal serum, cord serum, and milk were sampled for 65 Michigan mothers potentially exposed to PBBs. They showed a wide range of PBB concentrations and a strong bioaccumulation of PBBs in human milk (Table 1.12; Landrigan *et al.*, 1979).

In 1993, PBBs and other persistent compounds were measured in the serum of people who reported eating at least one meal per week of sport fish caught in the Great Lakes. The overall mean serum PBB concentration in 30 subjects was 0.4 µg/L. When stratified by lake, serum concentrations were highest for people who ate fish from Lake Huron (mean, 0.6 µg/L; range, 0.1–1.7 µg/L), followed by Lake Michigan (mean, 0.4 µg/L; range, 0.04–1.0 µg/L) and Lake Erie (mean,

Table 1.9 Estimates of daily exposure to PBBs from food in Europe

Population	Food category	PBB congener	Average consumers (pg/kg bw per day)		High consumers (pg/kg bw per day)	
			LB	UB	LB	UB
Infants	Human milk	PBB-153	[620, 920]	[920, 1400][a]	–	–
	Ready-to-eat meal	PBB-153	–	0.17, 0.64[b]	–	–
Children aged 1–3 yr	Milk and dairy products	PBB-52	0.34	16.1	0.69	32.1
		PBB-101	0.41	16.2	0.82	32.3
Children aged 3–6 yr	Fish and other seafood	PBB-49	0.76	0.88	3.28	3.79
		PBB-52	2.44	2.50	10.4	10.7
		PBB-77	0.01	0.01	0.04	0.06
		PBB-101	0.90	1.08	3.86	4.63
		PBB-153	0.47	11	2.01	47
	Meat and meat products	PBB-52	0.23	1.66	0.42	2.97
		PBB-101	0.23	1.66	0.42	2.97
Adults	Fish and other seafood	PBB-49	0.39	0.45	1.97	2.28
		PBB-52	1.23	1.26	6.27	6.45
		PBB-77	0.01	0.01	0.03	0.03
		PBB-101	0.46	0.54	2.32	2.78
		PBB-153	0.24	5.53	1.21	28.2
	Meat and meat products	PBB-52	0.1	0.74	0.25	1.76
		PBB-101	0.1	0.74	0.25	1.76
	Milk and dairy products	PBB-52	0.05	1.91	0.1	4.84
		PBB-101	0.04	1.91	0.12	4.86
Adults; specific groups of the population	Fish with > 8% fat; daily intake of 179 g fishmeat	PBB-49	–	–	9.61	11.22
		PBB-52	–	–	34.4	35
		PBB-77	–	–	0.06	0.09
		PBB-101	–	–	12.2	14.1
		PBB-153	–	–	4.33	89
	Supplements with fatty acids daily intake of 15 mL	PBB-49	–	–	2	10.4
		PBB-52	–	–	3	4.5
		PBB-77	–	–	0.01	0.02
		PBB-101		–	3	4.8
		PBB-153	–	–	3.8	18.9

[a] Results reported from a study in Finish and Danish human milk samples, respectively (Shen *et al.*, 2008); the values refer to the mean intake for average and high consumers.

[b] Those estimates refer to two upper bound exposures estimated from the only two available consumption surveys.

bw, body weight; LB, lower bound; PBBs, polybrominated biphenyls; UB, upper bound; yr, year

From EFSA (2010)

0.2 µg/L; range, 0.06–0.7 µg/L). When stratified by state, serum concentrations were highest for residents of Michigan (mean, 0.7 µg/L; range, 0.11–1.7 µg/L), followed by Ohio (mean, 0.2 µg/L; range, 0.06–0.7 µg/L) and Wisconsin (mean, 0.05 µg/L; range, 0.04–0.06 µg/L). The stronger contrasts by state are consistent with Michigan dairy products being the source of PBB contamination and with Wisconsin producing most of its own dairy products (Anderson *et al.*, 1998). [Michigan's Lower Peninsula has long shorelines on Lake Michigan and Lake Huron, and a very short shoreline on Lake Erie. Water from Lake Michigan drains into Lake Huron, which drains

Table 1.10 Serum concentrations of PBBs in residents exposed as a result of the Michigan incident

Population group	Participation rate (%)	*n*	Serum concentration (μg/L)		
			Range	Mean	Median
PBB chemical workers and their families	78.0	216	0–1240	43.0	4.5
Residents on quarantined farms	95.6	1750	0–1900	26.9	4.0
Direct recipients of food products from quarantined farms	95.1	1114	0–659	17.1	3.0
Residents on farms with PBB contamination below quarantine limits	95.0	44	1–13	3.5	2.0
Self-referred residents on farms with PBB contamination below quarantine limits or persons who had eaten food produced on such farms	–	242	0–24	3.5	2.0
Self-referred volunteers who had no direct connection with contaminated farms	–	273	0–111	3.2	1.0
Total		3639	0–1900	21.2	3.0

n, total number; PBBs, polybrominated biphenyls
From Landrigan *et al.* (1979). Copyright (c) 1979, John Wiley and Sons.

into Lake Erie. The Pine River, which borders the Michigan Chemical Corporation plant, flows into Lake Huron (Fig. 1.3).]

Serum PBB concentrations were measured in two cohorts of Michigan children: a "farm exposure" cohort consisting of 87 children enrolled in long-term studies of PBB- or PCB-contaminated farm products and a "fish exposure" cohort consisting of 236 children born to women who had consumed PBB-contaminated fish from Lake Michigan. Serum PBB concentrations were measured in the early 1980s when the children were aged 4 years. The percentages of children in the farm and fish exposure cohorts who had detectable serum PBBs (> 1 μg/L) were 21% and 13%, respectively. Significant predictors of serum PBB concentrations in children aged 4 years were weeks of nursing, PBB concentrations in maternal milk, and PBB concentrations in cord serum (Table 1.13; Jacobson *et al.*, 1989).

In the Michigan Long-Term PBB Study, 27% of children born to mothers exposed to PBBs through contaminated food had detectable serum PBB concentrations (> 1 μg/L). Risk factors for detectable serum PBB concentrations were maternal serum concentrations of 8 μg/L or more, nursing for 5.5 months or more, maternal age at childbirth of 28 years or more, and being born during the period of PBB exposure. Infants who nursed for 5.5 months or more were six times more likely to have detectable concentrations of

Table 1.11 Distribution of serum concentrations of PBBs in people exposed as a result of the Michigan incident

Group	*n*	Percentage with each group of serum concentrations (%)				
		0–1.1 μg/L	1.1–9.9 μg/L	10–99.9 μg/L	100–999 μg/L	> 1000 μg/L
PBB chemical workers	55	0	51	31	13	5
Farm residents	524	23	59	14	4	0.4
Random male farmers and consumers	109	12	64	17	6	1

PBBs, polybrominated biphenyls
Adapted from Anderson *et al.* (1978a)

Table 1.12 Concentrations of PBBs in maternal serum, cord serum, and breast milk in residents exposed as a result of the Michigan incident

Group	*n*	PBB concentration (μg/L)			Ratio to maternal serum (range)
		Range	Mean	Median	
Maternal serum	52	0–1150	26.2	2.5	–
Cord serum	58	0–104	3.2	1.0	7.04[a] (1.5–10.3)
Milk (lipid basis)	32	32–93 000	3614	225	122.0 (62.2–256.7)

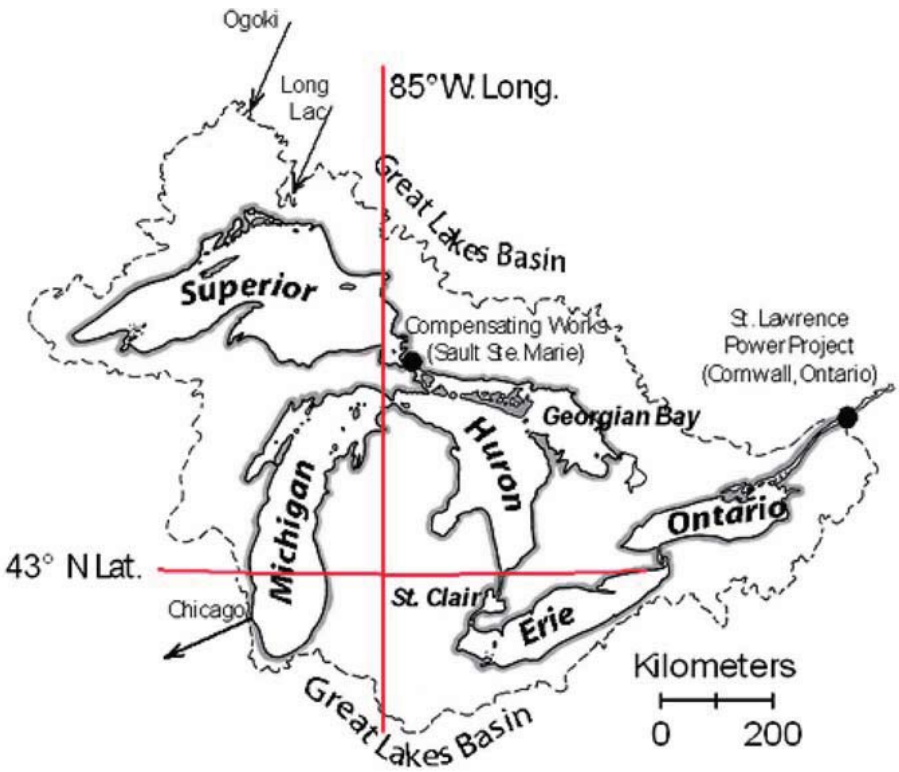
[a] [7.04 was reported by the authors, but this may refer to an inverse ratio]
PBBs, polybrominated biphenyls
Adapted from Landrigan *et al.* (1979). Copyright © 1979, John Wiley and Sons.

serum PBBs (95% CI, 2.0–19.6) (Joseph *et al.*, 2009).

Three out of nine samples of human hair [inferred to be from near the Michigan or the New Jersey PBB plant] contained PBBs at concentrations of 0.03, 1, and 2 ppm (Archer *et al.*, 1979).

Apart from the Michigan incident, several surveys have reported concentrations of the congener PBB-153 in the general population (Table 1.14). Analysis of data from *National Health and Nutrition Examination Survey* (NHANES) 2003–2004 indicated that PBB-153 was detected in 83% of samples (Sjödin *et al.*, 2008). Nonetheless, analysis of archived serum pools indicated that PBB-153 concentrations had been decreasing in the USA, the only country

Fig. 1.3 The Great Lakes basin area



From NOAA, Great Lakes Environmental Research Laboratory (GLERL, 2014)

Table 1.13 Serum concentrations of PBBs in children (age 4 years) born to Michigan mothers who ate contaminated farm products or fish

Cohort	*n*	Percentage of mothers with serum concentration > 1 ng/mL (%)	Serum concentration (ng/mL)	
			Mean	Range
Exposure from farm products	80	21.3	2.95	1.0–9.5
Exposure from fish	205	12.7	2.44	1.0–6.4

PBBs, polybrominated biphenyls
Adapted from Jacobson *et al.* (1989)

with multiple reports; in contrast, concentrations of the PBDEs that replaced PBBs have been increasing (Sjödin *et al.*, 2004b). One survey from Sweden reported much lower levels of PBBs than in the USA (Sjödin *et al.*, 2001). [A difficulty in interpreting PBB-153 concentrations is that this congener co-elutes with PBDE-154.]

In 2007, PBBs were detected in 90% and 50%, respectively, of maternal plasma and umbilical-cord plasma samples from women in Denmark with median PBB-153 concentrations of 181 and 68.6 pg/g lipid weight (Frederiksen *et al.*, 2010).

In 2003, PBB concentrations in human adipose tissue were collected from 20 women undergoing surgery for malignant and benign diseases in Spain. The mean sum of concentrations of seven PBB congeners was 0.358 ng/g lipid, with PBB-153 contributing 79% (Fernandez *et al.*, 2007). The ratio between human serum and adipose concentrations was estimated to be between 1:140 and 1:260 (Hakk & Letcher, 2003).

In 2007, PBB concentrations were measured in human hair collected from four villages in China where electronic-waste disassembly sites were located. Operations included recovering metals by burning cables, stripping metals in open-pit acid baths, and removing electronic components from circuit boards by heating over a grill, resulting in leakage, evaporation, runoff, and leaching of chemicals. PBB concentrations were elevated in two of these villages, compared with a control village 30 km away where there were no electronic-waste operations. Mono-, di-, and tribromobiphenyls predominated, with PBB-2 being by far the single most abundant congener (Table 1.15; Zhao *et al.*, 2008). In tissue samples of cancer patients in the same area, PBBs were detected in all samples of kidney, liver, and lung (n = 19, 55, and 7 samples, respectively). Median concentrations of PBBs in these tissues were 194, 193, and 145 ng/g lipid, respectively (Zhao *et al.*, 2009).

PXBs were detected in milk from seven mothers in Japan, 5 and 30 days after delivery. TEQs, calculated as a weighted sum of the concentrations of five non-*ortho* congeners, ranged from 0.42 to 1.41 pg/g (Ohta *et al.*, 2007). In a second study, five dioxin-like PXBs were measured in 20 mothers in Japan, 1 week after delivery. The sum of concentrations of five non-*ortho* congeners ranged from 12 to 350 pg/g lipid weight, with an average of 57 pg/g. The authors suggested that seafood was an important source of these congeners, as 3′,4′,5′-tribromo-3,4-dichlorobiphenyl was a major congener seen in fish and in human milk (Ohta *et al.*, 2008a).

PXBs were detected in milk from nine mothers in Madrid, Spain. The sum of concentrations of five non-*ortho* and three mono-*ortho* congeners was 0.45 pg/g lipid weight (Gómara *et al.*, 2011).

1.5 Occupational exposure

Historically, workers involved in the production of PBBs, PBB-containing plastics, and PBB-containing plastic products could have

Table 1.14 Concentrations of PBB-153 in human serum from surveys not directly related to the Michigan incident

Group, country	Year	*n*	Concentration (ng/g lipid)		Reference
			Median	Range	
Blood donors, USA	1988	12	19 pmol/g	4.2–84	Sjödin *et al.* (2001)
Female cleaners, Sweden	1997	20	0.59 pmol/g	0.25–1.4	Sjödin *et al.* (2001)
Archived serum pools, USA	1985–9	9	8.0	2.6–9.4	Sjödin *et al.* (2004b)
	1990–4	14	5.3	1.0–8.6	
	1995–9	10	4.7	1.9–10	
	2000–2	7	3.3	1.4–5.5	
NHANES, persons aged ≥ 12 years, USA	2003–4	2062	2.3	–	Sjödin *et al.* (2008)

n, total number; NHANES, National Health and Nutrition Examination Survey; PBB, polybrominated biphenyl

been exposed to PBBs via inhalation of dust and vapour, and/or via dermal contact.

After the Michigan incident in 1973, several studies showed that workers in PBB industries were exposed to high concentrations of PBBs. Several of these studies also showed high exposure among workers on dairy farm from the surrounding areas (Bekesi *et al.*, 1979a; Landrigan *et al.*, 1979; Stross *et al.*, 1979, 1981; Wolff *et al.*, 1979b). The Michigan population was more highly exposed than populations in other states.

In one PBB-manufacturing plant in the USA, 8 hour time-weighted average (TWA) air concentrations of PBB of 0.18 and 0.23 mg/m^3 were reported in 1977 (Bialik, 1982). These samples were collected in the manufacturing area and comprised mostly decabromobiphenyls. Surface-wipe measurements showed concentrations of up to 8 mg/100 cm^2. One surface-wipe sample collected on top of a table in the eating area had 0.1 mg/100 cm^2, which showed that in addition to inhalation and dermal routes of exposure, hand-to-mouth exposure was also possible. At the time of the survey, 95% of plant production consisted of decabromobiphenyl (18%) and decabromobiphenyl oxide (77%).

Several studies reported PBB concentrations in serum and adipose tissues (Table 1.16). Analysis of blood from employees at a hexabromobiphenyl-manufacturing company showed concentrations from 0.015 mg/L (after 3 months of exposure) to 0.085 mg/L (after 26 months of exposure) ($n = 6$), and of 0.006 mg/L in a supervisor employed for 38 months (Kay, 1977).

A study of exposure among PBB-manufacturing workers at another plant in the USA presented a detailed comparison of serum PBB concentrations by type of work activity (Bahn *et al.*, 1980a). A significantly higher number of PBB workers had detectable PBB concentrations compared with other workers (steelworkers and wiremen; 35.9% compared with 12.2%); also, the PBB workers had significantly higher serum PBB concentrations.

A clinical study including 55 exposed Michigan farm residents, 11 Michigan chemical workers and 46 non-exposed Wisconsin farmers showed that 7 out of 10 non-production workers (who did not participate in the production and handling of PBBs) had plasma concentrations of < 1 ng/mg (0.13–0.23 ng/mg protein) (Bekesi *et al.*, 1979a), while four production workers (who worked in the production and bagging section of the plant for several years, having been directly exposed to PBBs) had a PBB plasma concentration of around 10 ng/mg protein.

Clinical findings were reported for workers ($n = 55$) who manufactured Firemaster BP-6 from 1970 to 1974 in the USA (Anderson *et al.*, 1978a).

Table 1.15 PBB concentrations in human hair collected in villages around electronic waste-disassembly sites in China

Village	*n*	Concentrations (ng/g)	
		Median	Range
Tongshan	8	26	18–41
Panlang	11	29	14–55
Xiazheng	9	44	20–66
Xinqiu	8	58	24–103
Yandang (control)	4	26	22–32

PBBs, polybrominated biphenyls
Adapted from Zhao *et al.* (2008)

Other halogenated fire retardant chemicals were also produced at this plant. All 250 employees were invited to participate in the study, in particular those who had worked directly in the PBB-production area. Serum PBB concentrations were reported in ranges: 28 workers had serum PBB concentrations of 1.1–9.9 mg/L, 17 workers had 10–99.9 mg/L, 7 workers had 100–999.9 mg/L, and three workers were above 1000 mg/L.

In a study of liver function among farmers (n = 364) in Michigan after the accident, Anderson *et al.* (1978b) found the distribution of serum PBB concentrations to be: non-detectable–0.2 μg/L, 16 farmers; 0.21–1.0 μg/L, 69 farmers; 1.1–5.0 μg/L, 169 farmers; 5.1–10.0 μg/L, 52 farmers; and > 10.0 μg/L, 58 farmers.

One study assessed the distribution of PBB homologues (penta-, hexa-, and heptabromobiphenyls) in sera from dairy farmers and chemical-manufacturing workers. The relative concentration of two pentabromobiphenyls, both found in the Firemaster FF-1, differed widely between the two groups (Wolff & Aubrey, 1978). This would suggest different levels of exposure to the same mixture, but also that the mixture had been transformed between PBB manufacture and reaching the dairy farm, different routes of exposure, with farmers ingesting PBB partially metabolized in the animal food source. Compared with the original chemical product, one pentabromobiphenyl congener was not found in serum, possibly due to its relative ease of metabolism and excretion.

In the early 1990s, China started to process imported electronic waste ("e-waste") such as scrap metals, obsolete electric capacitors, household appliances, electric generators, and cable wires. Currently, 90% of all e-waste is imported from Japan, the USA, western European countries, and the Russian Federation. The recycling operations involve open-air burning, acid leaching, and physical dismantling by hammer, chisel, screwdriver, and bare hands. In 2008–2009, Chinese workers in the e-waste recycling industry were surveyed for serum levels of thyroid hormone, thyrotropin (thyroid-stimulating hormone), and brominated flame retardant (Wang *et al.*, 2010b). Workers exposed occupationally to brominated flame retardant during dismantling and recycling activities, non-occupationally exposed people, and controls were included in the study. The concentration of PBBs in sera of these occupationally exposed workers was 3.02 ng/mL plasma (n = 239). This value was lower than for farmers in the area surrounding the e-waste site [ΣPBB, 4.34 ng/mL plasma (n = 39)], but higher than for the controls [ΣPBB, 1.43 ng/mL plasma (n = 116)].

Table 1.16 Concentrations of PBBs in serum and adipose tissue of occupationally exposed workers

Year	Group	*n*	Concentration in µg/L				Reference
			Geometric mean	Median	Range	Limit of detection	
Serum – farm workers							
1976	Exposed farm workers	46	14	NR	1–180	NR	Stross *et al.* (1979)
Serum – chemical manufacturing[a]							
1975	Workers	7	NR	NR	6–85	NR	Kay (1977)
1976	Workers	28	48	NR	NR	NR	Stross *et al.* (1981)
1976	Workers, all	55	NR	NR	1.1–1729	NR	Wolff & Aubrey (1978), Wolff *et al.* (1979a)
	Production workers	10	603.9	108.4	NR	1	
	Non-production workers	45	16.5	6.1	NR	1	
1976	Workers	14	230	12	1–1530	< 0.2	Wolff *et al.* (1979b)
1978	Workers	14	227	22	1–1363	< 0.2	Wolff et al. (1979b)
1976–7	Workers and families	216	43.0	4.5	ND–1240	1	Landrigan *et al.* (1979)
1975–80	Workers (men)	29	25.4	20	1–1200	1	Eyster *et al.* (1983)
1978	Workers	35	NR	NR	ND–1340	NR	Bahn *et al.* (1980a, b)
1979	Production workers	4	NR	NR	10–10.2	1	Bekesi *et al.* (1979a)
1979	Non-production workers	7	NR	NR	0.13–0.23	1	Bekesi et al. (1979a)
Serum – e-waste recycling							
2008–9	Workers	236	*ΣPBB*				Wang *et al.* (2010b)
			3.02	NR	NR	NR	
			PBB-209				
			0.34	NR	ND–2.54	NR	
			PBB-103				
			0.67	NR	ND–4.96	NR	
			PBB-77				
			2.01	NR	ND–189.17	NR	
Adipose tissue – chemical manufacturing[a]					*(µg/kg)*		
1976	Production workers	7	196 490	46 940	5 000–580 000	500	Wolff *et al.* (1979a)
	Non-production workers	20	3880	2490	500–10 000	500	
1975–80	Workers (men)	29	5290	6000	400–350 000	1	Eyster *et al.* (1983)
NR	Workers	25	9330	NR	[300–80 000]	NR	Brown *et al.* (1981)
NR	Workers	28	NR	NR	12 820	NR	Stross *et al.* (1981)

[a] All plants studied were in Michigan and manufactured primarily "hexabromobiphenyl", except for the study by Bahn *et al.* (1980b), which studied a plant in New Jersey manufacturing mono- and deca-bromobiphenyl.
ND, not detected; NR, not reported; PBBs, polybrominated biphenyls

1.6 Regulations and guidelines

In 1974, the United States Food and Drug Administration established tolerance limits of 1.0 mg/kg (fat-weight basis) for PBBs in milk and meat fat, and 0.1 ppm in eggs, which were soon afterwards lowered to 0.3 mg/kg and 0.05 ppm, respectively (ATSDR, 2004).

In 1983, the European Union directed that PBBs may not be used in textile articles intended to come in contact with the skin (EFSA, 2010).

In 2002, the European Parliament directed that electrical and electronic equipment in the European Union may not contain PBBs at concentrations greater than 0.1%. Only six substances are restricted to such a degree, the other five being lead, mercury, cadmium, hexavalent chromium, and PBDEs. Plastic containing brominated flame retardants must be removed and treated separately from waste electrical and electronic equipment (EC, 2011).

The commercial product "hexabromobiphenyl" has been included in the Convention on Long-range Transboundary Air Pollution since 1998, and in the Stockholm Convention on Persistent Organic Pollutants since 2009. Parties to these conventions have agreed to take measures to eliminate the production and use of these pollutants (EFSA, 2010).

PBBs are not regulated as contaminants in food or as undesirable substances in animal feed. No other national or international regulations or guidelines were available.

2. Cancer in Humans

Data on the carcinogenicity of PBBs in humans are available from follow-up of a cohort of individuals in Michigan, USA, who were exposed as a result of an industrial incident in 1973 in which PBBs were accidentally mixed with cattle feed, and from one occupational study of chemical workers potentially exposed to several brominated compounds.

The Michigan cohort includes residents of contaminated farms, PBB-manufacturing workers, and people who consumed food from contaminated farms. The 3899 participants were followed by the Michigan Department of Public Health (Landrigan *et al.*, 1979). Two nested case–control studies were designed in this cohort. Hoque *et al.* (1998) evaluated the association between site-specific risks of cancer and serum PBB concentrations. In the follow-up of the cohort until 1993, 195 primary cancers were identified in 187 people. Controls were 696 randomly selected cancer-free individuals who were frequency matched to cases by sex and age. Baseline serum PBB concentrations were measured using standard methods. This study found a dose–response relationship for cancer of the digestive system (liver, stomach, oesophagus, pancreas). Odds ratios (ORs) for digestive cancers were 8.23 (95% CI, 1.27–53.3), 12.3 (95% CI, 0.80–191), and 22.9 (95% CI, 1.34–392), respectively, for serum PBB categories of 4–20 ppb, 21–50 ppb, and > 50 ppb after adjustment for age, sex, family cancer history, cigarette smoking, alcohol drinking, and baseline serum PCB concentration. Odds ratios for cancer of the breast based on the same categorization of exposure were 2.41 (95% CI, 0.92–6.30), not estimable due to zero exposed cases, and 1.39 (95% CI, 0.16–12.5). The analysis for serum PBB concentration and risk of lymphoma adjusted for all covariates except family history and baseline serum PCB concentration also showed a dose–response relationship, with corresponding odds ratios of 3.85 (95% CI, 0.32–46.2), 19.6 (95% CI, 1.52–253), and 48.9 (95% CI, 4.09–585). [This was a unique cohort that provided important information about the effects of PBBs. Positive associations were observed, but quantitative interpretation of the findings was hampered by small numbers, particularly in the analysis of lymphoma, where the referent group contained

only one case, leading to very wide confidence intervals. The excess risk for cancers of the digestive system was based on small numbers of cases at a wide variety of sites.]

Henderson *et al.* (1995) further examined the association between cancer of the breast and serum PBB concentration in a case–control study with 1925 women enrolled in the Michigan cohort. Twenty women who developed cancer of the breast were matched on race and age to 290 control women. The risk of cancer of the breast was elevated among women with serum PBB concentrations of 2.0–3.0 ppb (OR, 3.3; 95% CI, 0.8–13), and 4.0 ppb or greater (OR, 3.2; 95% CI, 0.8–13) compared with women with < 2.0 ppb after adjustment for body-mass index (BMI), history of cancer in a female relative, and other risk factors for cancer of the breast. [This study was informative despite its small size, given the paucity of information available on populations exposed to PBBs.]

Wong *et al.* (1984) conducted a mortality study in a historical cohort of white male chemical workers employed between 1935 and 1976. The workers' potential exposure to several chemicals, including PBBs, was categorized as more highly exposed (routine exposure) and less exposed (non-routine exposure). No detailed analysis of PBB exposure was presented. A total of 91 workers were classified as potentially exposed on a routine basis, and none died during the study period; among the 237 non-routinely exposed workers, 2 deaths were observed versus 6.4 expected, one of which was due to cancer of the large intestine (standardized mortality ratio, SMR, 10, [95% CI, 0.3–55]). This case of cancer of the large intestine was observed among 87 people who worked in the research laboratories and were classified as non-routinely exposed to PBBs (SMR, 80.4 [95% CI, 2.53–557]). [The study was uninformative because of the crude exposure classification and the small number of deaths in the PBB-exposed workers.]

3. Cancer in Experimental Animals

PBBs were previously evaluated for carcinogenicity in experimental animals (IARC, 1978, 1986). In the 1978 evaluation, the Working Group determined that there was inadequate evidence to classify PBBs. However, the 1986 evaluation determined that there was *sufficient evidence* in experimental animals for the carcinogenicity of commercial mixtures of PBBs. Since that time, new data had become available, and were taken into account in the present evaluation. Only data from original research have been summarized in the tables.

3.1 Mouse

See Table 3.1

3.1.1 Oral administration

The United States National Toxicology Program (NTP) studied the carcinogenic potential of Firemaster FF-1 (see Section 1 for composition) in mice when administered orally (NTP, 1983). Groups of 50 male and 50 female B6C3F$_1$ mice were given Firemaster FF-1 at a dose of 0 (corn oil), 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg body weight (bw) per day by gavage on five consecutive days per week for 6 months. The mice were then observed for an additional 18 months after treatment, i.e. 24 months in total (lifetime observation). There was a statistically significant increase ($P < 0.01$) in the incidence of hepatocellular carcinoma in males and females at 10 mg/kg bw per day: 21 out of 22 (95%) versus 12 out of 25 (48%; controls) in males; 7 out of 8 (88%) versus 0 out of 13 (controls) in females. The incidence of hepatic neoplasms appeared to be dose-dependent. Liver tumours were observed primarily in those groups of mice to which FF-1 was given in doses sufficient to induce hepatic toxicity. There was a trend towards an increase in the incidence of thyroid follicular cell adenoma in females treated

Table 3.1 Studies of carcinogenicity with PBBs in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Oral administration				
Mouse, B6C3F$_1$ (M, F) 30 mo Gupta *et al.* (1983a), NTP (1983), Silberhorn *et al.* (1990), EFSA (2010)	Firemaster FF-1 at 0 (corn oil), 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg bw per day in corn oil, 5 d/wk, for 25 wk; observed for total of 24 mo 50 mice/group; age 7–8 wk	*Males* Neoplastic nodules: 2/25 (8%), 1/27 (4%), 4/24 (17%), 2/25 (8%), 2/23 (9%), 1/22 (5%) Hepatocellular carcinoma: 12/25 (48%), 8/27 (30%), 8/24 (33%), 12/25 (48%), 15/23 (65%), 21/22 (95%)* *Females* Hepatocellular adenoma: 0/13, 2/19 (11%), 0/15, 1/11 (9%), 1/17 (6%), 1/8 (12%) Hepatocellular carcinoma: 0/13, 0/19, 2/15 (13%), 2/11 (18%), 3/17 (18%), 7/8 (88%)*	 *$P < 0.01$ *$P < 0.01$	Firemaster FF-1 blended with 2% calcium trisilicate Hyperplasia/adenoma of the follicular cells of the thyroid was not considered a major finding because of the small sample size and low incidence. Shortened survival time in mice at 10.0 mg/kg bw per day.
Mouse, C57BL/10ScSn (M) 12 mo Smith *et al.* (1990, 1995)	Inferon (iron-dextran): 600 mg/kg, s.c., followed by Firemaster BP-6 in diet [dose, NR] for 2 mo, followed by control diet for 10 mo Group 1: Fe (–) Group 2: Fe (+) Group 3: Fe (–) + Firemaster BP-6 Group 4: Fe (+) + Firemaster BP-6 7–19 mice/group; age 7–10 wks	Hepatocellular carcinoma: 0/15, 0/16, 0/7, 0/7 Hepatocellular nodules: 0/15, 0/16, 1/7 (14%), 4/7 (57%)	 NS	Purity, NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Transplacental and perinatal exposure				
Mouse, B6C3F_1 (M, F) 2 yr Chhabra *et al.* (1993), NTP (1993)	Perinatal exposure (F_0): Firemaster FF-1 at 0, 3, 10, or 30 ppm in feed from 60 d before breeding until weaning of the F_1 generation. Adult exposure (F_1): F_1 given same diet as F_0 through gestation, lactation, and 4 wk after weaning (age 8 wk), then diets containing Firemaster FF-1 at 0, 3, 10, or 30 ppm, 7 d/wk for 105 wk F_0:F_1 – 0:0, 0:10, 0:30 ppm (adult exposure only) F_0:F_1 – 0:0, 30:0 ppm (perinatal exposure only) F_0:F_1 – 0:10, 10:10, 30:10 ppm (perinatal plus adult exposure) F_0:F_1 – 0:30, 30:30 ppm (perinatal plus adult exposure) 60 mice/group	**F_0:F_1 – 0:0, 0:10, 0:30 ppm (adult exposure only)**		Purity, NR All mice at 0:30 or 30:30 ppm died before the end of the study. The survival of females at 30:10 ppm was lower than that of controls. Survival of males at 3:3 ppm was greater than that of controls. Other microscopic changes included hepatocyte cytomegaly, fatty change, clear cell focus, eosinophilic focus, hepatocyte necrosis, bile duct hyperplasia and hepatocyte cytological alteration.
		Males		
		Hepatocellular adenoma: 9/50 (18%), 48/49 (98%)*, 42/50 (84%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Hepatocellular carcinoma: 8/50 (16%), 30/49 (61%)*, 36/50 (72%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Hepatocellular adenoma or carcinoma (combined): 16/50 (32%), 48/49 (98%)*, 48/50 (96%)*	*$P < 0.001$ $P < 0.0001$ (trend)	
		Females		
		Hepatocellular adenoma: 4/50 (8%), 39/50 (78%)*, 46/48 (96%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Hepatocellular carcinoma: 1/50 (2%), 22/50 (44%)*, 35/48 (73%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Hepatocellular adenoma or carcinoma (combined): 5/50 (10%), 42/50 (84%)*, 47/48 (98%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		F_0:F_1 – 0:0, 30:0 ppm (perinatal exposure only)		
		Males		
		Hepatocellular adenoma: 9/50 (18%), 31/50 (62%)	$P < 0.001$	
		Hepatocellular carcinoma: 8/50 (16%), 17/50 (34%)	$P = 0.03$	
		Hepatocellular adenoma or carcinoma (combined): 16/50 (32%), 40/50 (80%)	$P < 0.001$	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 2 yr Chhabra et al. (1993), NTP (1993) (cont.)		*Females*		
		Hepatocellular adenoma: 4/50 (8%), 19/50 (38%)	$P < 0.001$	
		Hepatocellular carcinoma: 1/50 (2%), 4/50 (8%)	NS	
		Hepatocellular adenoma or carcinoma (combined): 5/50 (10%), 21/50 (42%)	$P < 0.001$	
		F$_0$:F$_1$ – 0:10, 10:10, 30:10 ppm (perinatal + adult exposure)	**Effect of perinatal exposure on the effect of adult exposure at 10 ppm (compared with 0:10)**	
		Males		
		Hepatocellular adenoma: 48/49 (98%), 46/49 (94%), 48/50 (96%)	NS	
		Hepatocellular carcinoma: 30/49 (61%), 31/49 (63%), 40/50 (80%)*	*$P = 0.01$	
		Hepatocellular adenoma or carcinoma (combined): 48/50 (98%), 46/49 (94%), 48/50 (96%)	NS	
		Thyroid follicular cell adenoma: 0/49, 0/48, 5/48 (10%)*	*$P = 0.02$ $P = 0.003$ (trend)	
		Females		
		Hepatocellular adenoma: 39/50 (78%), 38/50 (76%), 47/50 (94%)*	*$P = 0.005$ $P < 0.001$ (trend)	
		Hepatocellular carcinoma: 22/50 (44%), 26/50 (52%), 44/50 (88%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Hepatocellular adenoma or carcinoma (combined): 42/50 (84%), 44/50 (88%), 50/50 (100%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Thyroid follicular cell adenoma: 1/50 (2%), 1/50 (2%), 2/50 (4%)	NS	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 2 yr Chhabra et al. (1993), NTP (1993) (cont.)		**F_0:F_1 – 0:30, 30:30 ppm (perinatal + adult exposure)**	**Effect of perinatal exposure on adult exposure at 30 ppm (compared with 0:30)**	
		Males		
		Hepatocellular adenoma: 42/50 (84%), 48/50 (96%)	$P = 0.007$	
		Hepatocellular carcinoma: 36/50 (72%), 35/50 (70%)	NS	
		Hepatocellular adenoma or carcinoma (combined): 48/50 (96%), 50/50 (100%)	NS	
		Females		
		Hepatocellular adenoma: 46/48 (96%), 41/47 (87%)	NS	
		Hepatocellular carcinoma: 35/48 (73%), 29/47 (62%)	NS	
		Hepatocellular adenoma or carcinoma (combined): 47/48 (98%), 47/47 (100%)	NS	
Initiation–promotion				
Mouse, CD1 (F) 30 wk Berry *et al.* (1978, 1979)	Initiated with topical application of 200 nmol DMBA in acetone. After 1 wk, mice received 2 µg TPA, or 100 µg Firemaster BP-6, 2×/wk for 30 wk Groups: DMBA only TPA only DMBA + TPA DMBA + Firemaster BP-6 Firemaster BP-6 only 30 mice/group; age 6–8 wks	Skin papilloma: 0/30, 1/30 (3%), 28/30 (93%), 0/30, 0/30		Purity, NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, HRS/1 hairless (F) 20 wk Poland *et al.* (1982)	Mice (age 8 weeks) initiated with a single dose of MNNG (5 µmol in 50 µL of acetone) or vehicle applied to the dorsal skin, then 2 mg of Firemaster FF-1 (in 50 µL of acetone), 2×/wk for 5 wk, then 1 mg for 15 wk; PBB-153 or PBB-169, 20 µg in 50 µL of acetone 2×/wk topically for 20 wk. MNNG + FF-1, PBB-153-only, and MNNG-only groups: 26 mice/group MNNG + PBB-153, MNNG + PBB-169, PBB-169-only, and FF-1-only groups: 20 mice/group	Skin papilloma: MNNG only: 0/23 (0) MNNG + FF-1: 9/15 (60%)* (2.0)* MNNG + PBB-153: 0/20 MNNG + PBB-169: 12/20 (60%)* × (1.5)* FF-1 only: 1/16 (6%) (0.13) PBB-153 only: 0/22 PBB-169 only: 0/20	* Significant increase in incidence or multiplicity	Purity, NR Statistical analysis, NR

bw, body weight; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; M, male; MNNG, *N*-methyl-*N*′-nitro-*N*-nitroguanine; mo, month; NR, not reported; NS, not significant; PBBs, polybrominated biphenyls; s.c., subcutaneous; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; wk, week

with FF-1, but the incidences were low and the numbers of animals were small.

Groups of 7–19 male Ah-responsive C57BL/10ScSn mice received a single dose of iron-dextran (600 mg/kg) and were then fed a diet containing Firemaster BP-6 [dose not reported] for 2 months, followed by the control diet for 10 months. Hepatocellular nodules were observed in one mouse given Firemaster BP-6 only. Pre-treatment with iron-dextran did not have a significant synergistic effect on the induction of hepatocellular tumours (Smith *et al.*, 1990). [The limitations of the study precluded its use in the evaluation process.]

3.1.2 Transplacental and perinatal exposure

The NTP conducted studies of carcinogenicity in male and female B6C3F_1 mice given diets containing PBBs (Firemaster FF-1) to determine: (i) the effects of PBBs in mice receiving adult (F_1) exposure only from age 8 weeks for 2 years [conventional study of carcinogenicity]; (ii) perinatal (F_0) exposure only (dietary exposure of dams before breeding, and throughout gestation and lactation) followed by control diet for 2 years; and (iii) the combined effect of perinatal and adult exposure (Chhabra *et al.*, 1993; NTP, 1993).

Groups of 60 female mice were exposed to Firemaster FF-1 at a dietary concentration of 0, 3, 10, or 30 ppm for 60 days before breeding. After breeding to previously unexposed males, exposure continued throughout pregnancy and lactation. Weaning occurred on postnatal day 28, and dietary exposure at these same concentrations continued until the pups were approximately age 8 weeks. Subsequently, groups of 60 male and 60 female pups (F_1) were given Firemaster FF-1 at the same dietary concentrations (0, 3, 10, or 30 ppm) and continued on these diets for up to 2 years. After 9 months, 10 mice per group were evaluated.

At 9 months, hepatocellular adenomas occurred in one or more male and female mice from each exposure group, with a significant increase in incidence in the group at 30:30 ppm. A hepatocellular carcinoma occurred in one female mouse in the group at 30:30 ppm.

After 2 years, the effect of adult exposure [conventional study of carcinogenicity] was determined by comparing the groups at 0:0, 0:10 and 0:30 ppm. The incidences of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) were significantly increased ($P \leq 0.01$) in mice at 0:10 and 0:30 ppm. While a single hepatocellular adenoma or carcinoma occurred in tumour-bearing control mice, multiple adenomas, carcinomas, or both adenomas and carcinomas were often present in exposed mice. The effects of perinatal exposure only were determined by comparing the groups at 0:0 and 30:0 ppm. The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased ($P \leq 0.001$) in mice at 30:0 ppm. The effects of perinatal exposure plus adult exposure were determined by comparing the groups at 0:10, 10:10 and 30:10 ppm, and the groups at 0:30 and 30:30 ppm. When mice were exposed to the lower adult dose, there was a significant increase in the incidence of hepatocellular adenoma and carcinoma in females, and of carcinoma in males (Chhabra *et al.*, 1993; NTP, 1993).

3.1.3 Initiation–promotion

In an initiation–promotion study, groups of 30 female CD1 mice were initiated with a skin application of 200 nmol of 7,12-dimethylbenz[*a*]anthracene (DMBA) in acetone, or acetone only. One week later, the mice received topical applications of 2 µg of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) or 100 µg of Firemaster-BP6 in acetone, twice per week for 30 weeks. Firemaster-BP6 alone did not induce or promote

DMBA-initiated skin tumours (Berry *et al.*, 1978; Berry *et al.*, 1979).

Poland *et al.* (1982) investigated whether Firemaster FF-1 could promote *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)-initiated skin tumours in female HRS/1 hairless mice, as part of a larger study examining the skin tumour-promoting activity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), PCBs, and polychlorinated dibenzofurans (PCDFs). At age 8 weeks, mice were given a single topical dose of MNNG (5 µmol in 50 µL of acetone), or the vehicle only. Mice were then given a topical dose of Firemaster FF-1 (2 mg in 50 µL of acetone) twice per week for 5 weeks, then 1 mg for 15 weeks; or 2,2′,4,4′,5,5′-hexabromobiphenyl (PBB-153) or 3,3′,4,4′,5,5′-hexabromobiphenyl (PBB-169), 20 µg or 50 µL of acetone, respectively, twice per week for 20 weeks. There were 26 mice in the MNNG + FF-1, PBB-153-only, and MNNG-only groups; and 20 mice in the MNNG + PBB-153, MNNG + PBB-169, PBB-169-only, and FF-1 only groups. Tumours were classified as skin papillomas. Firemaster FF-1 and PBB-169 increased the incidence and multiplicity of MNNG-initiated tumours. [Statistical analysis was not reported.]

3.2 Rat

See Table 3.2

3.2.1 Oral administration

The NTP studied the carcinogenic potential of PBBs when administered orally in rats (NTP, 1983). Groups of 50 male and female Fischer F344 rats were given Firemaster FF-1 at a dose of 0 (corn oil), 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg bw per day by gavage on five consecutive days per week for 6 months. The rats were then observed for an additional 24 months (lifetime observation). The incidence of hepatocellular carcinoma was significantly increased ($P < 0.01$) in males and females at 10 mg/kg bw per day – males, 7 out of 31 (23%) versus 0 out of 33 (controls), and females, 7 out of 20 (35%) versus 0 out of 20 (controls) – and in males at 3 mg/kg bw per day – 7 out of 33 (21%) versus 0 out of 33 (controls). There was also a significant increase ($P < 0.01$) in the incidence of cholangiocarcinoma in females at 10 mg/kg bw per day – 7 out of 20 (35%) versus 0 out of 21 (controls) – and a slight increase ($P = 0.06$) in males at 10 mg/kg bw per day – 2 out of 31 (6%) versus 0 out of 33 (controls). The incidences of hepatic neoplastic nodules in female rats at 3 mg/kg bw per day and higher were significantly increased ($P < 0.01$). There was no clear effect of treatment on the incidence of hepatic neoplastic nodules in males. Liver tumours were observed primarily in rats to which Firemaster FF-1 was given in doses sufficient to induce hepatic toxicity. An increased incidence of myelomonocytic leukaemia was also observed in male rats at 0.3 mg/kg bw per day. [The Working Group noted that the spectrum of neoplastic lesions in the liver was similar to that associated with exposure to PCB-126 and PCB-118 in NTP studies, and hypothesized that the effect observed could be due to PCB activity or the presence of impurities that had dioxin-like activity.]

In a series of studies, Kimbrough *et al.* (1981) dosed non-inbred female Sherman rats with Firemaster FF-1. In one study, groups of 65 female rats were given a single dose of PBBs at 1000 mg/kg bw by gavage and observed for 24 months. The incidence of hepatocellular (trabecular) carcinoma and hepatic neoplastic nodules [adenomas] was significantly increased – 24 out of 58 (41%) versus 0 out of 53 (controls) and 42 out of 58 (72%) versus 0 out of 53 (controls), respectively. In a second study, groups of 30 female rats were given Firemaster FF-1 at a dose of 100 mg/kg bw by gavage twice per week for two 3-week periods separated by approximately 10 weeks (total of 12 doses). After 24 months observation, the incidences of hepatocellular (trabecular) carcinoma and hepatic neoplastic nodules were significantly increased – 17 out of

Table 3.2 Studies of carcinogenicity with PBBs in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344/N (M, F) 29 mo Gupta *et al.* (1983a), NTP (1983), Silberhorn *et al.* (1990), EFSA (2010)	Firemaster FF-1 at 0 (corn oil), 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg bw per day, 5 d/wk by gavage for up to 25 wk, and then observed for 23 mo without exposure 51 rats/group; age 7–8 wk	*Males* Neoplastic nodules: 0/33, 0/39, 1/40 (2%), 4/31 (13%)*, 4/33 (12%), 1/31 (3%) Hepatocellular carcinoma: 0/33, 2/39 (5%), 0/40, 1/33 (3%), 7/33 (21%)*, 7/31 (23%)* Cholangiocarcinoma: 0/33, 0/39, 0/40, 0/31, 0/33, 2/31 (6%)* Myelomonocytic leukaemia: 3/33 (9%), 5/39 (13%), 8/40 (20%)*, 4/31 (13%), 2/33 (6%), 2/32 (6%) *Females* Neoplastic nodules: 0/20, 2/21 (10%), 0/21, 2/11 (18%), 5/19 (26%)*, 8/20 (40%)* Hepatocellular carcinoma: 0/20, 0/21, 0/21, 0/11, 3/19 (16%), 7/20 (35%)* Cholangiocarcinoma: 0/20, 0/21, 0/21, 0/11, 0/19, 7/20 (35%)* Myelomonocytic leukaemia: 5/20 (25%), 4/21 (19%), 4/21 (19%), 1/11 (9%), 2/19 (11%), 4/20 (20%)	*$P < 0.05$ *$P < 0.01$ *$P = 0.06$ $P < 0.01$ (trend) *$P < 0.05$ *$P < 0.01$ $P < 0.01$ (trend) *$P < 0.01$ $P < 0.01$ (trend) *$P < 0.01$ $P < 0.01$ (trend) NS	Purity, NR Dose-dependent decrease in survival in males; survival in males at ≥ 0.3 mg/kg bw was significantly less ($P < 0.01$) than controls. Other microscopic lesions included atypical foci and bile duct hyperplasia in liver. [The Working Group noted that the same spectrum of neoplastic lesions in the liver was seen in a long-term NTP study using PCB-126 or PCB-118 (see Section 3, *Monograph* on Polychlorinated Biphenyls in this Volume).]
Rat, Sherman (F) Study I: 23 mo Study II: 24 mo Study III: 22 mo Kimbrough *et al.* (1981), Silberhorn *et al.* (1990), EFSA (2010)	*Study I:* Single dose of 1000 mg/kg bw Firemaster FF-1 or corn oil (control); 65 rats/group; age 2 mo *Study II:* corn oil (control), or 100 mg/kg bw Firemaster FF-1 2×/wk every 3 wk, total of 12 doses; 30 rats/group; age 2 mo *Study III:* Single dose of 200 mg/kg bw Firemaster FF-1 or corn oil (control); 16 rats/group; age 4 mo	*Study I* Liver Trabecular carcinoma: 0/53, 24/58 (41%) Neoplastic nodules: 0/53, 42/58 (72%) *Study II* Liver Trabecular carcinoma: 0/25, 17/28 (61%)	$P < 0.001$ $P < 0.001$ $P < 0.001$	Other non-neoplastic lesions included altered areas or foci, adenofibrosis and multinucleated hepatocytes in liver. Histological description of the neoplastic nodules was consistent with hepatocellular adenoma.

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sherman (F) Study I: 23 mo Study II: 24 mo Study III: 22 mo Kimbrough et al. (1981), Silberhorn et al. (1990), EFSA (2010) cont.)		Neoplastic nodules: 1/25 (4%), 24/28 (82%)	$P < 0.001$	
		Adenocarcinoma: 0/25, 1/28 (4%)	NS	
		Haemangioma: 1/25 (4%), 0/28	NS	
		Total malignant tumours: 0/25, 19/28 (68%)	$P < 0.001$	
		Study III		
		Liver: neoplastic nodules: 0/19, 5/16 (31%)	$P = 0.013$	
Transplacental and perinatal exposure				
Rat, F344/N (M, F) 2 yr Chhabra *et al.* (1993), NTP (1993)	Perinatal exposure (F_0): Firemaster FF-1 at 0, 1, 3, 10 ppm in feed from 60 d before breeding until weaning of the F_1 generation. Adult exposure (F_1): same diet as F_0 during gestation, lactation, and for 4 wk after weaning (age 8 wk); then FF-1 at 0, 3, 10, or 30 ppm, 7 d/wk for 104 wk. 60 rats/group F_0:F_1 – 0:0, 0:10, 0:30 ppm (adult exposure only) F_0:F_1 – 0:0, 10:0 ppm (perinatal exposure only) F_0:F_1 – 0:10, 3:10, 10:10 ppm (perinatal plus adult exposure) F_0:F_1 – 0:30, 10:30 ppm (perinatal plus adult exposure)	**F_0:F_1 – 0:0, 0:10, 0:30 ppm (adult exposure only)** *Males* Hepatocellular adenoma: 1/50 (2%), 10/49 (20%), 38/50 (76%)	$P = 0.002$ (0:10) $P < 0.001$ (0:30) $P < 0.001$ (trend)	Purity, NR Other microscopic changes included hepatocyte hypertrophy, eosinophilic focus, oval cell hyperplasia, hepatocyte cytoplasmic vacuolation and bile duct fibrosis.
		Hepatocellular carcinoma: 0/50, 2/49 (4%), 19/50 (38%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Hepatocellular adenoma or carcinoma (combined): 1/50 (2%), 12/49 (24%)*, 41/50 (82%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Females Hepatocellular adenoma: 0/50, 10/50 (20%), 38/50 (76%)	$P = 0.001$ (0:10) $P < 0.001$ (0:30) $P < 0.001$ (trend)	
		Hepatocellular carcinoma: 0/50, 2/50 (4%), 4/50 (8%)	NS	
		Hepatocellular adenoma or carcinoma (combined): 0/50, 12/50 (24%)*, 39/50 (78%)*	*$P < 0.001$ $P < 0.001$ (trend)	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344/N (M, F) 2 yr Chhabra et al. (1993), NTP (1993) (cont.)		**F_0:F_1 – 0:0, 10:0 ppm (perinatal exposure only)**		
		Males		
		Hepatocellular adenoma: 1/50 (2%), 5/50 (10%)	NS	
		Females		
		Hepatocellular adenoma: 0/50, 0/50	NS	
		F_0:F_1 – 0:0, 0:10, 3:10, 10:10 ppm (perinatal plus adult exposure)	**Effect of perinatal exposure on the effect of adult exposure at 10 ppm (compared to 0:10)**	**Effect of total exposure on carcinogenicity (compared to 0:0)**
		Males		
		Hepatocellular adenoma: 1/50 (2%), 10/49 (20%), 13/50 (26%), 16/50 (32%)	NS	[$P < 0.01$ (3:10 and 10:10)]
		Hepatocellular carcinoma: 0/50, 2/49 (4%), 1/50 (2%), 1/50 (2%)	NS	NS
		Hepatocellular adenoma or carcinoma (combined): 1/50 (2%), 12/49 (24%), 14/50 (28%), 16/50 (32%)	NS	$P < 0.001$ (0:10, 3:10, 10:10)
		Females		
		Hepatocellular adenoma: 0/50, 10/50 (20%), 22/50 (44%), 35/50 (70%)	$P < 0.001$ (10:10)	$P < 0.001$ (0:10 and [3:10]) [$P < 0.0001$ (10:10)] [$P < 0.001$ (trend)]
		Hepatocellular carcinoma: 0/50, 2/50 (4%), 1/50 (2%), 8/50 (16%)	$P < 0.01$ (10:10)	[$P < 0.005$ (10:10)]
		Hepatocellular adenoma or carcinoma (combined): 0/50, 12/50 (24%), 22/50 (44%), 39/50 (78%)	$P = 0.03$ (3:10) $P < 0.001$ (10:10) $P < 0.001$ (trend)	$P < 0.001$ (0:10; 3:10; 10:10) [$P < 0.001$ (trend)]

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344/N (M, F) 2 yr Chhabra et al. (1993), NTP (1993) (cont.)		**F_0:F_1 – 0:0, 0:30, 10:30 ppm (perinatal plus adult exposure)**	**Effect of perinatal exposure on the effect of adult exposure at 30 ppm (compared with 0:30)**	**Effect of total exposure on carcinogenicity (compared with 0:0)**
		Males		
		Hepatocellular adenoma: 1/50 (2%), 38/50 (76%), 38/50 (76%)	NS	$P < 0.001$ (0:30 and [10:30])
		Hepatocellular carcinoma: 0/50, 19/50 (38%), 23/50 (46%)	NS	$P < 0.001$ (0:30 and [10:30])
		Hepatocellular adenoma or carcinoma (combined): 1/50, 41/50 (82%), 41/50 (82%)	NS	$P < 0.001$ (0:30 and 10:30)
		Females		
		Hepatocellular adenoma: 0/50, 38/50 (76%), 45/50 (90%)	NS	$P < 0.001$ (0:30) [$P < 0.0001$ (10:30)]
		Hepatocellular carcinoma: 0/50, 4/50 (8%), 22/50 (44%)	$P < 0.001$	[$P < 0.0001$ (10:30)]
		Hepatocellular adenoma or carcinoma (combined): 0/50, 39/50 (78%), 47/50 (94%)	$P < 0.05$	$P < 0.001$ (0:30 and 10:30)
Rat, Sherman (M, F) 24 mo Groce & Kimbrough (1984), EFSA (2010)	Pregnant females given corn oil or Firemaster FF-1 (200 mg/kg bw in corn oil) by gavage on d 7 and d 14 of pregnancy. Weaned pups (exposure through placenta and milk) assigned to: Approximately 50 pups/group	*Males*		Purity, NR Other recorded non-neoplastic lesions included foci or altered areas in liver, hepatic cysts, chronic nephrosclerosis, chronic nephritis, interstitial fibrosis and adenomatous hyperplasia in lung and testicular atrophy in males; and foci or altered areas and adenofibrosis in liver, cardiac interstitial fibrosis, chronic nephrosclerosis, interstitial fibrosis in lung, endometrial polyp and ovarian cyst in females.
		Hepatocellular (trabecular) carcinoma: 0/42, 4/41 (10%)	NS	
		Neoplastic nodules: 0/42, 2/41 (5%)	NS	
		Females		
		Hepatocellular trabecular carcinoma: 0/48, 3/51 (6%)	NS	
		Neoplastic nodules: 2/48 (4%), 9/51 (18%)	NS	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Initiation–promotion				
Rat, Sprague Dawley (F) 180 d Jensen *et al.* (1982), EFSA (2010)	Rats given NDEA at 10 mg/kg bw i.p., 24 h after partial hepatectomy (PH); then 30 d later fed diets containing PB at 500 ppm, or Firemaster BP-6, or PBB-153 at 10 or 100 ppm for 180 d. Controls included rats without PH or NDEA, but fed the same diets. Group 1: PH + NDEA Group 2: None Group 3: PH + NDEA + PB Group 4: PH + NDEA + 10 ppm PBB-153 Group 5: None + 10 ppm PBB-153 Group 6: PH + NDEA + 100 ppm PBB-153 Group 7: None + 100 ppm PBB-153 Group 8: PH + NDEA + 10 ppm BP-6 Group 9: None + 10 ppm BP-6 Group 10: PH + NDEA + 100 ppm BP-6 Group 11: None + 100 ppm BP-6 Three or six/group	Liver neoplastic nodules: 0/6, 0/3, 2/6 (33%), 3/6 (50%), 0/3, 5/6 (83%), 1/3 (33%), 6/6 (100%), 0/3, 6/6 (100%), 2/3 (66%)	$P < 0.05$ (groups 6, 8 and 10 vs group 1)	BP-6 purity, NR; PBB-153 purity, > 99.9% Rats given BP-6 or PBB-153 without PH or NDEA had few altered foci compared with those given PH or NDEA. PBB-153 increased the number of enzyme-altered foci. Limitations of the study included small number of rats and short duration (i.e. less than lifetime exposure).
Rat, Sprague Dawley (F) 480 d Jensen & Sleight (1986), EFSA (2010)	Single dose of NDEA at 10 mg/kg bw, 24 h after partial hepatectomy (PH); 30 d later given 0.1 mg PBB-153 or PBB-169 for 140 d, then basal diet for another 310 d Group 1: Basal diet Group 2: PH + NDEA Group 3: PBB-169 Group 4: PH + NDEA + PBB-169 Group 5: PBB-153 Group 6: PH + NDEA + PBB-153 Group 7: PBB-153 + PBB-169 Group 8: PH + NDEA + PBB-153 + PBB-169 6–12 rats/group	*All groups* Hepatocellular carcinoma: 0/6, 0/12, 0/6, 1/11 (9%), 0/6, 1/10 (10%), 0/6, 1/11 (9%) Hepatocellular nodules: 0, 0.11, 0, 0.25, 0, 1.94, 0, 3.85	$P < 0.05$ (group 6 and group 8)	PBB-153 purity, > 99%; PBB-169 purity, > 99% The combination of PBB-153 and PBB-169 caused a synergistic effect on the development of altered hepatic foci and hepatic nodules per cm^3 liver.

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Administration with known carcinogens				
Rat, Sprague Dawley (F) 57 wk Schwartz *et al.* (1980)	Firemaster BP-6 at 50 ppm; after 4 wk, AAF added at 300 ppm for up to 57 wk. Group 1: Basal diet Group 2: BP-6 Group 3: AAF Group 4: BP-6 + AAF 8 or 12 rats/group; age at start, NR	Hepatocellular carcinoma: 0/8, 0/12, 3/8 (37%), 5/12 (42%) Cholangiocarcinoma: 0/8, 0/12, 1/8 (12%), 0/12 Mixed liver carcinoma: 0/8, 0/12, 1/8 (12%), 0/12 Mammary gland, adenocarcinoma: 0/8, 1/12 (8%), 3/8 (37%), 0/12 Mammary gland, cystadenocarcinoma: 0/8, 0/12, 4/8 (50%), 2/12 (17%) Ear duct gland, squamous cell carcinoma: 0/8, 0/12, 5/8 (62%), 1/12 (8%) Lung (metastatic tumours): 0/8, 0/12, 1/8 (12%), 1/12 (8%)		Purity of AAF and BP-6, NR Small numbers of rats and short observation period.

AAF, 2-acetylaminofluorene; bw, body weight; d, day; F, female; h, hour; M, male; MCL, mononuclear cell leukaemia; mo, month; NDEA, *N*-nitrosodiethylamine; NR, not reported; PBBs, polybrominated biphenyls; PH, partial hepatectomy; wk, week; yr, year

28 (61%) versus 0 out of 25 (controls), and 24 out of 28 (82%) versus 1 out of 25 (4%; controls). In a third study, groups of 16 female rats were given Firemaster FF-1 as a single dose at 200 mg/kg bw by gavage. After 22 months, the incidence of hepatic neoplastic nodules was significantly increased – 5 out of 16 (31%) versus 0 out of 19 (controls).

3.2.2 Transplacental and perinatal exposure

The NTP conducted long-term studies of toxicity and carcinogenicity in male and female F344/N rats given diets containing PBBs (Firemaster FF-1) to determine: (i) the effects of PBBs in rats receiving adult (F_1) exposure only from age 8 weeks for 2 years [conventional study of carcinogenicity]; (ii) perinatal (F_0) exposure only (dietary exposure of dams before breeding and throughout gestation and lactation) followed by control diet for 2 years; and (iii) the combined effects of perinatal and adult exposure (Chhabra *et al.*, 1993; NTP, 1993).

Groups of 60 female rats were exposed to Firemaster FF-1 at a dietary concentration of 0, 1, 3, or 10 ppm for 60 days before breeding. After breeding to previously unexposed males, exposure continued throughout pregnancy and lactation. Weaning occurred on postnatal day 28, and dietary exposure at these same concentrations continued until the pups were approximately age 8 weeks. Subsequently, groups of 60 male and 60 female pups (F_1) were given Firemaster FF-1 at the same dietary concentrations (0, 3, 10, or 30 ppm) and continued on these diets for up to 2 years.

After 2 years, the effects of adult exposure [conventional study of carcinogenicity] were determined by comparing the groups at 0:0, 0:10 and 0:30 ppm. The incidences of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined) were all significantly increased in males and females of the groups at 0:10 and 0:30 ppm. The majority of male and female rats had multiple hepatocellular adenomas. The incidence of hepatocellular carcinoma was significantly increased in males at 0:30 ppm. Although the combined incidence of adenoma and carcinoma was similar for males and females, there were more carcinomas in males at 0:30 ppm (19 carcinomas) than in females (4 carcinomas). Multiple hepatocellular carcinomas occurred in seven males at 0:30 ppm. In the perinatal-only exposure study, the neoplastic effects of perinatal exposure were determined by comparing the groups at 0:0 and 10:0 ppm; marginal increases in the incidence of hepatocellular adenoma (1 out of 50, 5 out of 50) were noted in males. The effects of perinatal exposure plus adult exposure were determined by comparing the groups at 0:10, 3:10, and 10:10 ppm, and the groups at 0:30 and 10:30 ppm. The incidence of hepatic tumours in females was significantly greater than in those rats exposed only as adults. In females receiving varying concentrations at F_0 and a constant concentration of 10 or 30 ppm at F_1, the incidences of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined), increased significantly with the concentration given at F_0. The incidence of mononuclear cell leukaemia in males and females in the groups exposed either as adults only or both perinatally and as adults generally was significantly elevated compared with untreated controls, most notably at the higher exposures (Chhabra *et al.*, 1993; NTP, 1993).

In a study in pregnant Sherman rats given Firemaster FF-1 at an oral dose of 200 mg/kg bw on days 7 and 14 of gestation, the incidences of neoplastic nodules and hepatocellular carcinoma were slightly increased (not significantly) in male and female offspring over the 24 months after treatment (Groce & Kimbrough, 1984).

3.2.3 Initiation–promotion

To determine whether PBB mixtures or individual congeners could serve as tumour promoters in a two-stage test for hepatocarcinogenesis, groups of three or six female Sprague-Dawley rats were given *N*-nitrosodiethylamine (NDEA) as a single intraperitoneal dose at 10 mg/kg bw, 24 hours after a 70% partial hepatectomy. After 30 days, the rats were fed a basal diet or a basal diet containing Firemaster BP-6 or PBB-153 [called "HBB" in the article] at a concentration of 10 or 100 ppm for 180 days. Diets were prepared by adding phenobarbital, Firemaster BP-6 or PBB-153 in corn oil to a basal diet. Controls included non-hepatectomized rats or rats not given NDEA. At 100 ppm, Firemaster BP-6 alone caused an increase (two out of three rats; not statistically significant) in the incidence of neoplastic nodules. In combination with partial hepatectomy and NDEA, diets that contained Firemaster BP-6 or PBB-153 were associated with significant ($P < 0.05$) promotion of neoplastic nodules: five out of six rats receiving PBB-153 at 100 ppm, and six out of six rats receiving Firemaster BP-6 at 10 ppm, and six out of six rats receiving Firemaster BP-6 at 100 ppm. Both Firemaster BP-6 and PBB-153 increased the number of enzyme-altered foci (Jensen *et al.*, 1982). [The limited numbers of animals and less-than-lifetime observation period in this study limited the conclusions that could be reached on carcinogenic potential.]

To determine the effect of individual PBB congeners on the enhancement of gamma-glutamyl transpeptidase (GGT)-positive altered hepatic foci and the development of hepatic nodules and carcinomas, groups of 6 or 12 female Sprague-Dawley rats were given a single dose of NDEA, 24 hours after a 70% partial hepatectomy. After 30 days, the rats were fed a basal diet, or the basal diet containing PBB-153 at 10 ppm, PBB-169 at 0.1 ppm, or PBB-153 (10 ppm) + PBB-169 (0.1 ppm) for 140 days, followed by basal diet for an additional 310 days. Rats were killed 170, 240 or 480 days after partial hepatectomy. Dietary exposure to the PBB congeners alone or in combination did not increase the incidence of hepatocellular carcinoma, hepatic nodules, or altered hepatic foci. However, PBB-153 alone or in combination with PBB-169 increased the development of altered hepatic foci and nodules in partially hepatectomized rats given NDEA. Rats that had not been hepatectomized and given NDEA, and that were fed the basal diet or the basal diet containing PBB congeners, had no or relatively few altered hepatic foci when compared with rats that received the same diets but had been partially hepatectomized and given NDEA (Jensen & Sleight, 1986).

3.2.4 Administration with known carcinogens

Groups of 8 or 12 female Sprague-Dawley rats were given diets containing 2-acetylaminofluorene (AAF) at a concentration of 300 ppm, Firemaster BP-6 at 50 ppm, or BP-6 + AAF, for approximately 1 year. Firemaster BP-6 significantly reduced the incidence of AAF-induced tumours at non-hepatic locations (mammary gland and ear duct), but did not affect the incidence of hepatic tumours. Ingestion of Firemaster BP-6 only did not increase the incidence of tumours when compared with untreated controls (Schwartz *et al.*, 1980). [Conclusions regarding the carcinogenic potential of Firemaster BP-6 were limited by the low number of animals per group and the less-than-lifetime observation period.]

3.3 Hamster

See Table 3.3

Table 3.3 Studies of carcinogenicity with PBBs in hamsters

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Hamster, Syrian Golden (M) 273 d Wasito & Sleight (1989)	Initiated with NDEA as a single s.c. dose at 0 or 80 mg/kg bw, then fed diets containing BP-6 at 0 or 100 mg/kg for 140 days, after which basal diet was given until the end of the study W(d 273). Group 1: control Group 2: NDEA Group 3: NDEA + BP-6 Group 4: BP-6 30 hamsters/group	*Nasal cavity* Papilloma: 0/30, 1/30 (3%), 9/30 (30%), 0/30 Adenoma: 0/30, 2/30 (7%), 1/30 (3%), 0/30 Adenocarcinoma: 0/30, 7/30 (23%), 2/30 (7%), 0/30 Squamous cell carcinoma: 0/30, 0/30, 2/30 (7%), 1/30 (3%) Total nasal tumours: 0/30, 11/30 (37%), 15/30 (50%), 1/30 (3%) *Tracheal papilloma (multiplicity)*: 0, 26, 27, 0 (4.33, 1.6)	$P < 0.05$	Purity, NR Nasal tumours occurred at approximately the same incidence in hamsters given NDEA as in those given NDEA + BP-6.

bw, body weight; d, day; M, male; NDEA, *N*-nitrosodiethylamine; PBBs, polybrominated biphenyls; s.c., subcutaneous

Initiation–promotion

In an initiation–promotion study of carcinogenesis of the respiratory tract, groups of 30 male Syrian Golden hamsters were initiated with a single subcutaneous dose of NDEA at 0 or 80 mg/kg bw and were then (7 days later) fed a diet containing Firemaster BP-6 at 0 or 100 mg/kg for 140 days, followed by basal diet from day 140 until the end of the experiment at 273 days. Firemaster BP-6 slightly promoted the development of benign tracheal papilloma in hamsters. The multiplicity of tracheal papillomas, but not the incidence, was significantly increased in hamsters given NDEA + BP-6 compared with those given NDEA only. Tracheal papilloma was not seen in untreated hamsters or in hamsters fed a diet containing Firemaster BP-6 only. Nasal tumours (total) occurred at approximately the same incidence in hamsters given NDEA only or NDEA + BP-6. Adenomas occurred in the nasal cavity of two hamsters given NDEA only and in one hamster given NDEA + BP-6. Adenocarcinoma occurred in the nasal cavity of seven hamsters given NDEA only, and in two hamsters given NDEA + BP-6. Squamous cell carcinoma of the nasal cavity occurred in two hamsters given NDEA + PBBs and in one hamster given Firemaster BP-6 only (Wasito & Sleight, 1989).

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

PBBs share several chemical and physical characteristics with their chlorinated analogues, including effective absorption and distribution, the higher brominated biphenyls distributing/re-distributing to fatty tissues. PBBs readily cross the placenta in several species (DiCarlo *et al.*, 1978; Ecobichon *et al.*, 1983). PBBs have estimated long half-lives in animal tissues, serum, and fat, ranging from 22 days to more than 69 weeks (Miceli & Marks, 1981; Ecobichon *et al.*, 1983), extending to years in humans (ATSDR, 2004). PBBs have the potential to greatly alter their own distribution, metabolism, and

excretion through at least two mechanisms: PBB congeners are potent and efficacious inducers of xenobiotic-metabolizing enzymes, for which they may also become substrates and inhibitors (see Section 4.3).

4.2 Genetic and related effects

Limited data on PBBs and genotoxicity were available to the Working Group (reviewed in Silberhorn *et al.*, 1990). Firemaster BP-6, Firemaster FF-1, and the individual congeners PBB-77, -153, -169, and -153 + -180 have been tested in assays for genotoxicity. All assays with commercial PBB mixtures or individual congeners gave negative results for genotoxicity in mammals, except one in which a more-than-additive mitotic arrest response was seen in the bone marrow of pregnant rats treated with Firemaster [not further specified] and colchine (Ficsor & Wertz, 1976).

Only three PBB congeners have been tested in bacterial assays for mutation (Silberhorn *et al.*, 1990), i.e. the 2-, 3-, and 4-bromobiphenyls (PBB-1, PBB-2, PBB-3). All results were negative with and without metabolic activation (Haworth *et al.*, 1983), except PBB-3 that gave positive results with activation from S9 (Kohli *et al.*, 1978).

4.3 Biochemical and cellular effects

4.3.1 Induction of xenobiotic metabolism and oxidative stress

PBBs, like their chlorinated analogues, are ligands for several cellular and nuclear receptors. The earliest description of PCBs as ligands was for the aryl hydrocarbon receptor (AhR) (Bandiera *et al.*, 1982). This binding preceeded the efficacious induction of a broad spectrum of xenobiotic-metabolizing enzymes, most noticeably certain cytochrome P450-dependent monoxygenases (CYPs). PCBs and PBBs increased the activity of CYP2Bs and microsomal epoxide hydrolase (Parkinson *et al.*, 1983), glutathione transferases (Schramm *et al.*, 1985), and UDP-glucuronosyltransferase (Ahotupa & Aitio, 1978).

Of the individual PBB congeners, like PCB congeners with the same substitution pattern, the best ligands for AhR are those isomers and congeners in which halogens are present in the *meta* and *para* positions of biphenyl, but without *ortho* halogens (Robertson *et al.*, 1982, 1983, 1984b). These PBBs are referred to as "coplanar" or "dioxin-like" congeners, typical examples of which are PBB-77, PBB-126, PBB-169. Other halogenated biphenyls, characterized by halogen substitution in the *ortho* and *para* positions of biphenyl (e.g. 2,2′,4,4′,5,5′-hexabromobiphenyl, PBB-153), activate the constitutive androstane receptor (CAR). PBBs in this group induce CYP2B1/2 and as such resemble phenobarbital in their mode of induction of cytochrome P450 (Robertson *et al.*, 1982, 1984b; Parkinson *et al.*, 1983). PBBs with one *ortho* bromine may be mixed-type inducers of CYPs, inducing CYP1A and CYP2B subfamily members (Robertson *et al.*, 1981, 1982).

Although there is great similarity in the modes of induction of cytochrome P450 by PCBs and by PBBs, in terms of potency and efficacy there are a few examples of qualitative differences, and many quantitative differences. 3,4,4′-Tribromobiphenyl (PBB-37) is strictly an inducer of CYP1A in rat liver, while its chloro analogue also induces CYP2B isoforms (Robertson *et al.*, 1982; Parkinson *et al.*, 1983). Andres and co-workers compared the modes of induction and potency of a series of 3,3′,4,4′-tetrahalobiphenyl congeners in which each chlorine atom was sequentially replaced with bromine; the brominated analogues were more potent and more efficacious inducers of cytochrome P450 and much more toxic (Andres *et al.*, 1983).

In a 16-day time-course, Firemaster BP-6 was more efficacious than Aroclor 1254 (both at a dose of 500 mg/kg bw) in repressing hepatic

selenium-dependent glutathione peroxidase activity (Schramm *et al.*, 1985). Given that the average relative molecular mass of Firemaster BP-6 is almost twice that of Aroclor 1254, Firemaster BP-6 had a greater effect at about half the molar dose.

4.3.2 Substrates and inhibitors of xenobiotic metabolism

The metabolic activation of lower halogenated biphenyls to electrophiles and their reaction with cellular substituents, such as proteins and DNA, the production of oxygen-centred radicals, and the biological and toxicological consequences of these reactions, have been explored extensively with individual PCBs and commercial PCB mixtures. However, the same level of attention has not been paid to the PBBs, although it may be assumed that many of the same principles/pathways apply (see *Monograph* on Polychlorinated Biphenyls, Section 4.2 and Section 4.6, in this Volume).

Mills and coworkers investigated the metabolism of PBBs by hepatic microsomes from male rats treated with 3-methylcholanthrene [CYP1A inducer]. The rate of metabolism in decreasing order was PBB-15 (fastest), followed by PBB-37, PBB-77, PBB-56, PBB-70, and PBB-49. The rate of metabolism by hepatic microsomes from male rats treated with phenobarbital [an inducer of CYP2B] was PBB-4 (fastest) followed by PBB-49, PBB-52, PBB-56, PBB-70, and PBB-101. Thus CYP1A preferentially metabolized congeners with adjacent non-halogenated *ortho* and *meta* carbon atoms, while CYP2B preferentially metabolized congeners with adjacent non-halogenated *meta* and *para* carbons on at least one ring (Mills *et al.*, 1985). Also, PBB-169 effectively inhibited the metabolism of PBB-77 at similar concentrations (Mills *et al.*, 1985).

4.3.3 Cell–cell communication and metabolic cooperation

There were three reports that Firemaster BP-6 and individual PBB congeners can inhibit cell–cell communication or metabolic cooperation (Trosko *et al.*, 1981; Tsushimoto *et al.*, 1982; Kavanagh *et al.*, 1987). Firemaster BP-6, and PBB-118, PBB-153, PBB-180, and PBB-194 were reported to exert a dose-related inhibition of metabolic cooperation at concentrations that were relatively non-toxic to cells (Trosko *et al.*, 1981; Tsushimoto *et al.*, 1982). Firemaster BP-6 and PBB-153 displayed dose-dependent inhibition of cell–cell communication (Kavanagh *et al.*, 1987). In contrast, PBB-77, PBB-126, and PBB-169, all three with a dioxin-like activity, were inactive as inhibitors of metabolic cooperation or cell–cell communication at non-cytotoxic concentrations (Tsushimoto *et al.*, 1982; Kavanagh *et al.*, 1987).

4.3.4 Initiation–promotion

Six publications described studies that assessed Firemaster BP-6 and individual PBB congeners (PBB-77, PBB-153, PBB-169, and the combination of PBB-153 and PBB-169) as initiators and promoters of preneoplastic lesions in two-stage models of hepatocarcinogenesis in female Sprague-Dawley rats. All studies found that Firemaster BP-6 and individual PBB congeners were weak initiators, producing a small number of preneoplastic foci when administered alone. In contrast, Firemaster BP-6 and PBB -77, PBB-153, and the combination of PBB-153 and PBB-169 were generally efficacious promoters following an initiation regimen of partial hepatectomy plus NDEA, while PBB-169 alone did not show promoting activity (Jensen *et al.*, 1982, 1983, 1984; Jensen & Sleight, 1986; Rezabek *et al.*, 1987; Dixon *et al.*, 1988).

4.3.5 Other biochemical and cellular effects

In contrast to the PCBs, the PBBs had not yet been investigated for estrogenicity and anti-estrogenicity via estrogen-receptor binding (Gierthy *et al.*, 1997), effects on calcium channels via activation of the ryanodine receptor (Wong *et al.*, 1997), ability to cause insulin release from cells in culture (Fischer *et al.*, 1996), their potency in lowering cellular dopamine levels (Chu *et al.*, 1995), and their ability to activate neutrophils to produce superoxide (Fischer *et al.*, 1998).

4.4 Organ toxicity

In studies of acute toxicity, especially with dioxin-like PBBs, pathological and biochemical changes in the liver are evident in a matter of days. In rats, for example, a single intraperitoneal dose of PBB-77 at 150 µmol/kg resulted in a statistically significant increase in liver weight in 24 hours, and a significant decrease in thymus weight in 4 days (Robertson *et al.*, 1991). Small distinct lipid droplets in hepatocytes were seen histopathologically as early as day 2, while a loss of cortical lymphocytes of the thymus was seen at day 4.

In a 30-day study, mice and rats were given either Firemaster FF-1 or an equal molar equivalent of PBB-153 (Gupta *et al.*, 1981). After 15 days, livers were enlarged due to hepatocyte swelling, fatty infiltration, and proliferation of the endoplasmic reticulum, in animals treated with 3 or 30 mg/kg, and these hepatocellular alterations persisted to 120 days at the highest dose. Firemaster FF-1 was more toxic than PBB-153 (Gupta *et al.*, 1981).

In a long-term study, rats and mice were given Firemaster FF-1 or BP-6 for 6 months (Gupta *et al.*, 1983b; NTP, 1983). Treated rodents showed decreased body-weight gain (despite no change in feed consumption), increased liver weight, and decreased thymus weight. Microscopic changes in the liver included hepatocellular swelling, disorganization, single-cell necrosis, fatty infiltration, and bile-duct proliferation. Levels of hepatic porphyrin were markedly increased, while serum levels of T4 (thyroxine) and T3 (triiodothyronine) were decreased (Gupta *et al.*, 1983b; NTP, 1983). After the 6 months of dosing, the animals were observed for an additional 23 or 24 months. Treated rats showed significantly higher incidence of atypical hepatocellular foci, neoplastic nodules, hepatocellular carcinoma, and cholangiocarcinoma (see Section 3).

Mild microscopic changes in the thyroid gland were also observed in the NTP study (NTP, 1983). Kasza and colleagues carried out a more detailed examination of the effects of PBBs in the rat thyroid. On microscopic (light and electron) examination after short-term dietary exposure, they found ultrastructural lesions consistent with diminished synthesis and secretion of thyroxine (Kasza *et al.*, 1978).

In a subsequent NTP study (NTP, 1993), the effects of exposure to Firemaster FF-1 were investigated in rats and mice exposed as adults, exposed only perinatally (dietary exposure of dams before breeding and throughout gestation and lactation), or exposed both perinatally and as adults. The adult-only exposures demonstrated that the major organ affected by toxicity associated with PBBs was the liver. At 9 months, rats had decreased body weight, hepatomegaly, non-neoplastic histopathological changes, mild anaemia, increased serum cholesterol, and decreased serum triglycerides (males only) (NTP, 1993).

Immunocompetence after exposure to PBBs has been investigated in rodents and birds (Vos & Van Genderen, 1973; Luster *et al.*, 1978), in cattle (Jackson & Halbert, 1974; Kateley & Bazzell, 1978), in swine (Howard *et al.*, 1980), and in humans (Bekesi *et al.*, 1979b, 1987). Exposure of rats to dioxin-like PBBs resulted in rapid loss of cortical thymocytes (Robertson *et al.*, 1991), as described above. In rats exposed to PBBs, the ability to mount an antibody response to an

antigen was impaired. Both cell-mediated and humoral immunity were affected in rats and mice (Vos & Van Genderen, 1973; Luster *et al.*, 1978). Farm cattle given fodder contaminated with PBBs developed a range of symptoms, including atrophic thymus, abnormal lymph nodes, and prolonged infections (Jackson & Halbert, 1974). In contrast, Kateley & Bazzell (1978) did not find evidence of immune system impairment in cattle exposed environmentally, or exposed accidentally to PBBs at much lower levels. In sows fed Firemaster BP-6 at a dose of 100 or 200 ppm during the second half of lactation, the lymphocyte mitogenic response was significantly reduced in piglets tested at age 4 weeks (Howard *et al.*, 1980). In Michigan-farm residents who had consumed food contaminated with PBBs, immune-function abnormalities in vitro were evident in 20–25% (Bekesi *et al.*, 1987) and 35–40% (Bekesi *et al.*, 1979b) of the residents examined.

Endocrine disruption

Several investigations have reported PBB-related effects in individuals exposed during the Michigan poisoning episode of the 1970s (see Section 1.4.4). Dietary exposure to PBBs was associated with an elevated occurrence of self-reported abnormal Pap tests in women; occurrence was lower in exposed women who had breastfed for more than 12 months (Jamieson *et al.*, 2011). Maternal exposure to PBBs was also associated with increased likelihood of a male birth (Terrell *et al.*, 2009) and with increased infant birth weights (Sweeney & Symanski, 2007).

Perinatal exposure of rats to PBBs diminished the effect of exogenously administered estradiol on uterine weight and uterine RNA content. PBBs increased the hepatic microsomal metabolism of estradiol, estrone, and ethynylestradiol in vitro (McCormack *et al.*, 1979; Bonhaus *et al.*, 1981).

4.5 Mechanistic considerations

PBBs are highly lipophilic, and bioconcentrate and bioaccumulate. In mammals, they are transferred through the placenta and in breast milk (McCormack *et al.*, 1981; Kimbrough, 1985; Jacobson *et al.*, 1989). PBBs are efficacious inducers of hepatic metabolism, accelerating the turnover (half-lives) of endogenous and exogenous compounds. An imbalance in metabolizing enzymes may lead to increased oxidative stress through at least three mechanisms, which have been observed with PCBs. Firstly, it has been demonstrated that the persistent induction of CYPs, in the absence of substrate, may lead to the production of reactive oxygen species (Schlezinger *et al.*, 1999, 2000). Secondly, an increase in or induction of certain metabolizing enzymes, especially CYPs and epoxide hydrolase, may steer the metabolism of endogenous and exogenous compounds towards more redox-reactive intermediates, estradiol, PCBs, etc., and increase redox cycling (CYP reductase, DT-diaphorase) (Twaroski *et al.*, 2001). Lastly, a reduction in antioxidants and antioxidant enzymes, such as selenium and selenium-dependent glutathione peroxidase, may cause an increase in oxidative stress through the lowering of antioxidant defenses (Schramm *et al.*, 1985; Twaroski *et al.*, 2001; Lai *et al.*, 2010, 2011).

PBBs display a variety of adverse effects, including immune-system suppression (Bekesi *et al.*, 1979b, 1987), disruption of normal hormone function (McCormack *et al.*, 1979; Bonhaus *et al.*, 1981) and disruption of cell–cell communication. The liver and the immune system are early targets of PBB toxicity. PBBs are weak initiators of rodent two-stage hepatocarcinogenesis and are efficacious promoters in this model system. PBBs produce lesions in the liver and in a variety of other tissues and organs. Other acute adverse biochemical and toxic effects of PBBs are no doubt mediated by the interactions of various PBBs with other sites and cellular receptors.

Much less research has been conducted on PBBs than on PCBs. Commercial PBB mixtures are associated with equivalent or greater toxicity than their chlorinated analogues (Matthews *et al.*, 1978; Andres *et al.*, 1983). It is likely that the congeneric PBBs exhibit their toxicity and disease potential via many of the same pathways as their chlorinated counterparts.

5. Summary of Data Reported

5.1 Exposure data

Polybrominated biphenyls (PBBs) are a class of aromatic compounds consisting of 209 congeners, in which 1–10 bromine atoms are attached to a biphenyl nucleus. The current nomenclature arranges the 209 congeners by increasing numbers of bromine atoms from 1 to 209. PBBs are not known to occur naturally. PBBs are chemically comparable to the polychlorinated biphenyls (PCBs), although the bromine atom is larger than the chlorine atom, and the carbon–bromine bond is weaker than that between carbon and chlorine. PBBs are characterized by low volatility, which decreases with increasing number of substituted bromine, and low solubility in water; they are chemically stable and persistent in the human body, although to a lesser extent than PCBs. Highly brominated PBB congeners tend to debrominate to less brominated congeners.

The analytical methods for detection of PBBs are similar to those for PCBs, but highly sensitive methods are required at low concentrations.

PBBs were produced primarily as flame retardants, as hexa-, octa- and decabromobiphenyls, with bromine content of up to 85% by weight. PBBs were also added to plastics as flakes (up to 10%), and not chemically incorporated into the polymers. Other uses were in coatings and lacquers, and in polyurethane foam.

PBBs have been detected primarily near the sites of production and use; however, detection in biota of remote areas shows that PBBs should be considered as global environmental pollutants. One major episode of human food contamination occurred in Michigan, USA, in which animal feed supplement was contaminated with a commercial PBB mixture. The highest exposure occurred from consuming dairy products from those farms that had received the contaminated feed. As a result of this accident in 1973–1974, PBB production soon ceased in the USA; by 2000, all known production had ceased globally. Workers involved in production were exposed to PBBs through inhalation or dermal contact. Some workers continue to be exposed today through e-waste dismantling and recycling.

Mixed polybromochlorobiphenyls (PXBs) are a class of aromatic compounds with a mixed content of chlorine and bromine atoms attached to the biphenyl nucleus. PXBs have been observed as minor contaminants in some commercial PCB or PBB mixtures, and maybe formed upon disposal of these products at high temperature. PXBs have been detected in environmental and biological samples.

5.2 Human carcinogenicity data

Human data on the carcinogenicity of PBBs were available primarily from follow-up of residents exposed to contaminated food following an industrial accident in Michigan, USA. In a nested case–control analysis, positive findings were observed for lymphoma and cancers of the digestive system combined (including liver, stomach, oesophagus, and pancreas). The cohort was unique, but small, and the risk estimates are imprecise.

5.3 Animal carcinogenicity data

PBBs have been evaluated using a variety of study designs in rats, mice and hamsters, ranging in duration from several months up to 2 years.

These include complete studies of carcinogenicity, studies of carcinogenicity involving transplacental and perinatal exposure, studies assessing promoting activity, using tumours or preneoplastic lesions as an end-point, a study of co-carcinogenicity, and a study of modification of iron metabolism.

Firemaster FF-1, a commercial mixture of PBBs, was tested for carcinogenicity in two studies by gavage or in the diet in male and female mice: FF-1 caused a significant increase in the incidence of hepatocellular carcinoma. In another study of carcinogenicity incorporating adult-only, perinatal-only, and adult-plus-perinatal exposures, Firemaster FF-1 caused significantly increased incidences of hepatocellular adenoma and carcinoma, and hepatocellular adenoma and carcinoma combined. There was also a positive trend for thyroid follicular-cell adenoma in male mice.

Firemaster FF-1 was tested for carcinogenicity in two oral gavage studies in male and female rats: FF-1 caused significantly increased incidences of hepatic neoplastic nodules, hepatocellular carcinoma and (rare) cholangiocarcinoma in male and female rats, and myelomonocytic leukaemia in male rats. In another study of carcinogenicity incorporating adult-only, perinatal-only, and adult-plus-perinatal exposures, Firemaster FF-1 exposure caused significantly increased incidences of hepatocellular adenoma and carcinoma, hepatocellular adenoma and carcinoma combined, and mononuclear cell leukaemia in male and female rats.

In Syrian golden hamsters, Firemaster BP-6 in the diet promoted the development of *N*-nitrosodiethylamine-initiated benign nasal papillomas in one study. Firemaster BP-6 did not promote 7,12-dimethylbenz[*a*]anthracene-initiated skin tumours in one study in mice.

PBB-153 had promoting activity in two studies of *N*-nitrosodiethylamine-induced rat liver carcinogenesis with hepatic nodules and altered hepatic foci as the end-points, but did not have promoting activity in one study of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced mouse skin carcinogenesis.

PBB-169 had promoting activity in one study of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced mouse skin carcinogenesis, but did not have promoting activity in one study of *N*-nitrosodiethylamine-induced rat liver carcinogenesis, although it enhanced the liver tumour promoting activity when administered together with PBB-153.

5.4 Mechanistic and other relevant data

PBBs are highly lipophilic compounds that biocncentrate and bioaccumulate in fatty tissues. PBBs are efficacious inducers of hepatic metabolism, accelerating the turnover (reducing the half-lives) of both endogenous and exogenous compounds. PBBs display a variety of adverse effects including suppression of the immune system and disruption of normal hormone function. PBBs are weak initiators of two-stage hepatocarcinogenesis in rodents, but they are efficacious promoters in these model systems. When administered to rodents by themselves and for longer periods of time, PBBs are carcinogens that produce tumours in the liver and in a variety of other tissues and organs.

While there is an extensive body of literature to assess the carcinogenicity of PCBs (see the *Monograph* on Polychlorinated Biphenyls in this Volume), their brominated analogues have received much less attention and study. Firemaster, a commercial mixture of PBBs, causes aryl hydrocarbon receptor-related toxicity equivalent to or greater than that of their chlorinated analogues. PBBs likely will exhibit their toxicity and disease potential via many of the same pathways as their chlorinated counterparts.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of polybrominated biphenyls.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of Firemaster FF-1.

There is *limited evidence* in experimental animals for the carcinogenicity of polybrominated biphenyl-153.

There is *inadequate evidence* in experimental animals for the carcinogenicity of polybrominated biphenyl-169 and Firemaster BP-6.

6.3 Overall evaluation

Polybrominated biphenyls are *probably carcinogenic to humans (Group 2A)* on the basis of mechanistic similarities to polychlorinated biphenyls.

Rationale for the mechanistic upgrade of polybrominated biphenyls to Group 2A:

- Polybrominated biphenyls share several chemical and physical characteristics with their chlorinated analogues.
- Polybrominated biphenyls are effectively absorbed and distributed, cross the placenta and are detected in milk.
- Polybrominated biphenyls have estimated long half-lives in animal tissues, serum and fat.
- Polybrominated biphenyl congeners are potent and efficacious inducers of xenobiotic-metabolizing enzymes.
- Individual polybrominated biphenyl congeners inhibit cell-to-cell communication or metabolic cooperation.
- Individual congeners PBB-77, PBB-153, PBB-169 are weak initiators and efficacious promoters of two-stage hepatocarcinogenesis.
- Individual polybrominated biphenyls, as for their chlorinated analogues, are ligands for several cellular and nuclear receptors.
- In studies of acute toxicity, pathological and biochemical changes in the liver and thymus are evident in a matter of days.
- In long-term studies, polybrominated biphenyls induce microscopic changes in rodent liver, described as hepatocellular swelling, disorganization, single cell necrosis, fatty infiltration and bile duct proliferation, and mild microscopic changes in thyroid glands.
- Reduced immunocompetence after polybrominated biphenyl exposure was found in rodents, birds, cattle, swine and humans.
- Perinatal exposure of rats to polybrominated biphenyls diminished the effect of exogenously administered estradiol on uterine weight and uterine RNA content. Polybrominated biphenyls increased the hepatic microsomal metabolism of estradiol, estrone and ethynylestradiol in vitro.
- Polybrominated biphenyl exposure in women was also associated with increased odds of a male birth.

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