Key role of mechanistic data in recent evaluations of TCDD, PCBs and PBBs

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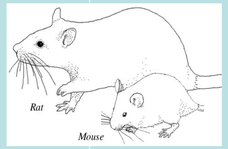
Cancer in humans

	TCDD	PCBs	PBBs
Cohort study populations	▪ Occupational settings (*US NIOSH study, BASF cohort, IARC multicountry cohort*) ▪ Accidental exposure of the general population (*Seveso, Italy*)	▪ Occupational settings (n=13) ▪ Accidental exposure of the general population (*Yusho, Yusheng*) (n=4) ▪ Populations with high dietary exposure (n=5) ▪ General population (n=15)	▪ Accidental exposure of the general population (Michigan, USA) (n=1)
Case-control studies	▪ Nested case-control studies within the IARC cohort for soft-tissue sarcoma and NHL	▪ cancer of the breast (n=32) ▪ NHL (n=17) ▪ Other sites (n=9)	N.A.
Sites with sufficient evidence in humans	▪ All cancers combined	▪ Cutaneous melanoma	N.A.
Sites with limited evidence in humans	▪ Lung ▪ Soft-tissue sarcoma ▪ NHL	▪ NHL (clear dose-response in several studies) ▪ Breast	N.A.
Other positive findings	N.A.	▪ Dose-response for cancers of the brain, prostate, stomach, and pancreas	▪ Combined digestive system (excluding colon and rectum) ▪ Lymphoma

Overall evaluations

Agent	IARC Group	Volumes
2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD)	1	15, 41, 69, 100F
3,3',4,4',5-Pentachlorobiphenyl (PCB 126)	1	100F
Polychlorinated biphenyls, dioxin-like, with a Toxicity Equivalency Factor (TEF) according to WHO (PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189) NB: Overall evaluation, upgraded to Group 1 with strong supporting evidence from mechanistic data	1	100F
Polychlorinated biphenyls	1	18, 107
Polybrominated biphenyls NB: Overall evaluation, upgraded to Group 2A with supporting evidence from mechanistic data, namely mechanistic similarity with polychlorinated biphenyls	2A	18, 107

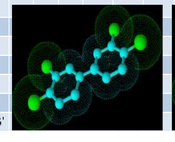
Cancer in experimental animals

	TCDD	PCBs: Individual congeners, binary mixtures, and fresh commercial products	PBBs: Individual congeners and fresh commercial products
			
Rat	Liver, biliary tract, lung, oral mucosa, hard palate /turbinates, tongue, thyroid gland, subcutaneous tissue, adrenal gland, pituitary gland, uterine cervix, pancreas, skin	Liver, biliary tract, lung, oral mucosa, thyroid gland, uterus Offspring: mammary gland (benign + malignant)	Liver, biliary tract, myelomonocytic leukaemia, mononuclear cell leukaemia
Mouse	Liver, lung, thyroid gland, lymphoma, subcutaneous tissue	Liver, lung, skin (topical) Offspring: promotion of lung tumours	Liver, thyroid gland; promotion of liver tumours

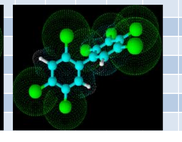
Chlorine position on the biphenyl rings and congener nomenclature (BZ)

Chlorine position 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	45	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

Coplanar biphenyl



Non-coplanar biphenyl



Dioxin-like PCBs (with a Toxic Equivalent Factor) are highlighted in red.

Historical perspective

- Since 1977, the *IARC Monographs* Programme has conducted several evaluations of the carcinogenic hazards of dioxins, polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) (see overall evaluations).
- In October 2009, in the frame of the re-evaluation of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) in volume 100F, PCB 126 was upgraded to Group 1 and the Working Group recommended an in-depth re-evaluation of agents with properties similar to TCDD.
- In February 2013, the *Monographs* programme conducted a re-evaluation of PCBs and PBBs.

Mechanistic data relevant to the carcinogenic potential of PCBs and PBBs

Coplanar and non-coplanar biphenyls

Non-coplanar biphenyls		Coplanar biphenyls
CAR/PXR	**Target receptor**	AhR
CYP2B1/2	**Induction of xenobiotic-metabolizing enzymes**	CYP1A1
Mutations, DNA strand-breaks, chromosomal aberrations	**Genetic and related effects**	DNA-adduct formation
Liver	**Organ toxicity**	Liver, skin
Metabolic activation and other mechanisms	**Immunotoxicity**	AhR-mediated
Driven by hydroxylated metabolites	**Endocrine effects**	AhR-mediated (steroid hormones)
	Carcinogenic potential	
	Cross potentiation of coplanar and non-coplanar biphenyls in combined carcinogenesis bioassays	

Upgrading PBBs based on similarities with PCBs

- Several shared chemical and physical characteristics
- Effectively absorbed and distributed across the placenta and detected in milk
- Long estimated half-lives in animal tissues, serum and fat
- Potent and efficacious inducers of xenobiotic–metabolizing enzymes
- Individual PBB congeners inhibit cell to cell communication or metabolic cooperation
- Individual PBB congeners are weak initiators and strong promoters of two-stage hepatocarcinogenesis
- Ligands for several cellular and nuclear receptors
- Pathological and biochemical changes in the liver and thymus within days in studies of acute exposure
- In studies of chronic exposure in rodents, microscopic changes in the liver, bile-duct proliferation, and mild microscopic changes in thyroid glands
- Reduced immunocompetence following PBB exposure in rodents, birds, cattle, swine, and humans
- Perinatal exposure in rats to PBBs diminished the effect of estradiol administered exogenously on uterine weight and uterine RNA content
- Increased microsomal metabolism of estradiol, estrone and ethynylestradiol *in vitro*
- Increased odds of a male birth following PBB exposure in women

OUTCOME AND IMPACT OF THE EVALUATIONS

- ✓ PCBs identified as priority agents in 2009 (IARC Technical Publication No. 42-*Identification of research needs to resolve the carcinogenicity of high-priority IARC carcinogens*, 2009)
- ✓ *IARC Monographs* volume 107 meeting on PCBs and PBBs publicized to the scientific community through an oral presentation (7th *International Workshop on PCBs*, Arcachon, France, May 2013)
- ✓ Contribution to the report by the Danish Health and Medicines Authority "Health risks of PCB in the indoor climate in Denmark" (in press)
- ✓ Publication of the outcome shortly after the meetings :
  - Baan R, Grosse Y, Straif K, **Secretan B**, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Galichet L, Cogliano V (2009). *Lancet Oncol* **10**,1143-4
  - **Lauby-Secretan MB**, Loomis D, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K (2013). *Lancet Oncol*, **14**, 287-8

HOW MECHANISMS COME INTO PLAY

- ✓ **TCDD** was the 2nd carcinogen to be classified in Group 1 without sufficient evidence in humans, on the basis of strong mechanistic data; first subsequently confirmed by *sufficient evidence in humans.*
- ✓ **PCB126** upgraded to Group 1 on the basis of extensive evidence showing activity identical to TCDD for every step of the mechanism described for TCDD-associated carcinogenesis in humans
- ✓ **"Dioxin-like" PCBs** upgraded to Group 1 on the basis of evidence showing activity similar to TCDD, and as a class of compounds similar to PCB126
- ✓ **"HOWEVER, the carcinogenicity of PCBs cannot be attributed solely to the carcinogenicity of the dioxin-like PCBs."**
- ✓ **PBBs** upgraded to Group 2A with mechanistic data, based on strong similarities with PCBs.
  - ➢ **Cascade of evaluations of individual compounds that have similarities in their biological activities, leading to a higher classification based on strong mechanistic evidence**

International Agency for Research on Cancer

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