III.9.2 Effects on mice

In chronic feeding studies with mice, the most noteworthy effects were on the liver (see below under Carcinogenesis and Appendix D). Daily dosage of mice with 1 mg KC-400 caused effects on the skin (loss of hair, erosion and ulceration after 3 months) in addition to enlargement of the liver and other pathologic changes (210).

No chronic studies of effects on reproduction have been reported, but a single dose of 20 mg/kg Clophen A60 lengthened oestrous cycles in mice (211).

III.9.3 Effects on dogs

A two-year chronic feeding study was conducted in beagle dogs exposed to 1, 10, and 100 ppm of Aroclors 1242, 1254 and 1260 in the diet (68, 212). Four dogs of each sex were included in each of the 9 feeding groups and in a tenth control group; the dogs were 4-7 months old at the start of exposure. Six dogs died during the experiment: of these three females died from chronic peritonitis (one on 100 ppm Aroclor 1242, one on 10 ppm Aroclor 1254, and one on 100 ppm Aroclor 1260). Table III.9.6 summarizes the principal findings at the end of the two-year exposure period: there were dose-related increases in liver weights, serum alkaline phosphatase levels, and leukocyte counts. The most noteworthy findings on gross pathologic observation were "numerous pinpoint nodules" in the stomachs of dogs in all treatment groups (except the 1 ppm Aroclor 1242 group). These nodules were observed in 22 of the 66 treated dogs,

Table III.9.6. Effects in dogs after two-year oral exposure to PCBs (from data in ref. 212)

	Leukocyte counts (thousands/mm^3)	Serum alkaline phosphatase KA units/100 ml	Liver weight, % of body weight	Pinpoint nodules in stomach
Controls (8)	11.45	5.22	3.51	0/8
Aroclor 1242:				
1 ppm (8)	12.44	4.48	3.26	0/8
10 ppm (7)	13.46*	5.93	3.62	3/7
100 ppm (7)	19.93***	5.91	3.87	4/7
Aroclor 1254:				
1 ppm (8)	14.26**	5.62	3.52	3/8
10 ppm (7)	14.19**	7.49	3.64	1/7
100 ppm (7)	20.59***	9.64**	4.11*	5/7
Aroclor 1260:				
1 ppm (8)	14.28	5.77	3.77	2/8
10 ppm (8)	14.69**	4.98	3.73	2/8
100 ppm (6)	12.11	30.22***	5.03**	2/6

*, $P < 0.05$; **, $P < 0.01$, ***, $P < 0.001$; significant differences from controls.

versus none in the 8 controls. No histopathological diagnoses of these lesions were included in the original report (212), but in 1975 it was reported that re-examination of the slides had shown evidence of "gastrointestinal inflammatory lesions and ulcerations which appeared similar to those reported by Allen (69) in rhesus monkeys".* Six of the dogs with stomach lesions, and two of the others, also had inflamed kidneys. The stomach lesions were equally prominent in dogs fed all three Aroclors, but the effect on liver weight was greatest in those fed Aroclor 1260 (Table III.9.6).

III.9.3 Effects on Non-human Primates

Rhesus monkeys are extremely susceptible to the effects of PCBs (69). Female monkeys fed 25 ppm Aroclor 1248 in the diet developed severe facial lesions and alopecia and had to be removed from the contaminated diet after 2 months. The five surviving females were still devoid of eyelashes and had facial acneform lesions two years later. Although several of these females conceived, all but one appeared to experience either fetal resorption or abortion. The one infant born was underweight (375 g versus 544 g) and had high levels of PCBs in the fat (28 ppm) and adrenals (24 ppm) (196).

Female monkeys given 2.5 and 5.0 ppm Aroclor 1248 in their diets developed facial edema, swollen eyelids, erythema, loss of hair, and acne within 2 months (213). By the fourth month, irregularities in the menstrual cycles and an increased level of urinary ketosteroids

* This statement, made at the National Conference (9), was deleted from Calandra's published paper (68), which states that "No remarkable histopathologic changes were found".

III.14. Carcinogenic and Co-Carcinogenic Effects

Studies of carcinogenic and co-carcinogenic effects of PCBs are reviewed in detail in Appendix D and only a brief summary is included here.

In a long-term study by Kimbrough et al. (266), Sherman rats fed 100 ppm Aroclor 1260 in the diet for 21 months developed hepatocellular carcinomas (26/184) and neoplastic nodules (144/184) in the liver, whereas 173 control animals developed only one carcinoma and no neoplastic nodules. The terminology used to describe the liver lesions is that developed at a recent workshop of experts in liver pathology (269), where some of the slides from the PCB-treated animals were reviewed. The study reported in ref. 266 followed a sequence of shorter-term studies in which the earlier stages of development of liver lesions in PCB-treated rats had been described (see Section III. 10.8); in one of these studies, liver nodules had been reported in the second generation of rats exposed to 20 ppm Aroclor 1254 at an age of only 330 days (179). Other significant findings in the livers of treated rats were adenofibrosis (cholangiofibrosis) (189) and abnormal pancreatic-type tissues (247). The significance of these findings is not clear. Adenofibrosis has been reported in the livers of rats fed with carcinogens (268); some experts believe that they have the potential to develop into cholangiocarcinomas (283), although an earlier review concluded that they were not convincingly pre-cancerous (284).

In another long-term study (207), groups of Charles River rats were fed with 1, 10, and 100 ppm Aroclor 1242, 1254, and 1260 for 24

months. Although the initial report indicated only mild liver lesions (207), a more recent review (68) reports the occurrence of lesions classified as nodular hyperplasia, hepatomas and cholangiohepatomas in 44/74 of the rats surviving near to the end of the experiment in the groups fed 100 ppm of all three Aroclors. Although there are some terminological problems and findings have not been adequately reported, these results appear consistent with those of Kimbrough et al. and suggest an oncogenic potential for all three Aroclors. There was also an excess incidence of pituitary tumors (chromophobe adenomas) in all treated groups in this experiment.

Other studies reviewed in Appendix D were conducted for much shorter periods and generally at higher dose levels; they constitute little more than preliminary screening tests. Kanechlors KC-500, KC-400, KC-300 induced nodular hyperplasia and cholangiofibrosis, but not hepatocellular carcinomas, in rats within 28-52 weeks (190). KC-400 induced multiple adenomatous nodules in the livers of rats within 400 days (271). Aroclor 1254 induced adenofibrosis and hepatomas in mice fed for only 6-11 months (191). KC-500 induced nodular hyperplasia and hepatocellular carcinoma in mice within 32 weeks, whereas KC-400 and KC-300 did not do so within the same period (192).

These six studies are consistent in showing that PCB mixtures with 42-60% chlorine content induce neoplastic and pre-neoplastic lesions in the livers of rats and mice, and that this induction is very rapid at high dietary levels (250-500 ppm). Because most of the studies have been terminated early, the full development of the lesions

has not yet been studied. No long-term feeding studies have yet been reported which have failed to show some evidence of neoplastic change: the longest such study was terminated after 12 months (69).

Among co-carcinogenic studies conducted in vivo, KC-500 markedly promoted or accelerated the hepatocarcinogenicity of α-BHC and β-BHC in mice (192). However, KC-400 did not promote the development of cervical carcinomas in mice induced by methylcholanthrene (272), and KC-500 inhibited or delayed the hepatocarcinogenicity of three other carcinogens in rats (273).

Numerous studies have shown that PCBs, by stimulating the cytochrome P-450 dependant mixed function oxidase system in the mammalian liver, can activate secondary carcinogens and mutagens or de-activate primary carcinogens and mutagens. Pretreatment with PCBs markedly increases liver injury by vinyl chloride, a known human liver carcinogen, but decreases injury by 1,1-dichloroethylene (274). PCBs promote the metabolism of dimethylnitrosamine to an active mutagen (281, 282), but de-activate a primary carcinogen (MNNG). PCBs are exceptionally efficient stimulators of the mixed function oxidase system and are now used routinely to activate suspect carcinogens in bacterial mutagenesis bioassays (276, 280).

PCBs are known to stimulate the mixed function oxidase system at extremely low doses (219) and their action in doing so is potentiated by other environmental pollutants such as BHC and DDT (246).

In addition to their direct carcinogenic effects and co-carcinogenic effects, the immunosuppressive effects of PCBs are also expected to be important in potentiating the action of other carcinogens.

parafollicular cell tumor of the thyroid gland, whose incidance was reduced from 37/160 to 18/166 ($P < 0.01$). It is not clear whether this reduction should be attributed to chance occurrence among the 17 organs examined, or whether it should be related to the known affects of PCBs on thyroid function (Section III.12.3).

D-2 Industrial Bio-Test Experiment with Charles River Rats.

This experiment was described in an unpublished report dated November 1971 (207) and a brief summary of results was presented at the National Conference on Polychlorinated Biphenyls in November 1975 (68). One thousand Charles River strain albino rats were divided into 10 treatment groups. 100 rats (50 male and 50 female) served as common controls; 100 rats (50 male and 50 female) were included in each of nine exposed groups, fed diets containing 1, 10 and 100 ppm of Aroclors 1242, 1254 and 1260 respectively. Dosage started when the animals were about 4-6 weeks old (mean weights 133-136 g) and continued for 24 months. However, 5 males and 5 females were sacrificed from each treatment group for interim studies after 3, 6 and 12 months, so that each treatment/sex subgroup contained only 35 animals at the start of the second year. Mortality was high, especially in the animals fed 100 ppm (Table D1), so that only 6-21 animals from each treatment/sex subgroup survived to the terminal sacrifice at 24 months (i.e., when the animals were about 25 months old). The original report gives summaries of body weights, food consumption, clinical chemistry, organ weights, and histopathological

diagnoses for each of the 20 subgroups. As in the experiment of Kimbrough et al., the principal effects were noted in the liver and in tumor incidence: these are summarized from th original report (207) in Tables D1 and D2.

Table D1 summarizes data on survival, liver weight, and tumor incidence. Liver weights were significantly increased in the animals fed 100 ppm (except the males fed Aroclor 1242); the effect was largest with Aroclor 1254. The incidence of tumors was similar in all groups, except for chromophobe adenomas of the pituitary, which were not found in controls but were found in 8 of the 9 treated groups and in 12 of the 18 subgroups. The number of surviving animals was too small to compare individual groups with controls, but if all the treated animals are considered together the increased incidence approaches statistical significance. Almost all of these pituitary tumors were found in the animals killed at 24 months, but 3 were found in animals dying at 20-23 months.

Table D2 summarizes the histopathologic findings reported in the original report (207) for the livers of control animals and those treated at 100 ppm. These diagnoses were summarized by the original pathologist as follows:

> Significant liver injury was found in animals fed 100 ppm Aroclor 1260 (T-III). The compound associated lesions consisted of vacuolar change, focal hypertrophy and focal hyperplasia. In addition, there were lesions of inflammation, necrosis, fibrosis and minor degeneration in this group which, although seen in the controls and lower test groups, were more severe and frequent in the T-III group.

Table III. Industrial Bio-Test Rat Experiment: Basic Results.

Group	Sex	No. at 12 mo.	Survival to month 18	21	24	Liver % of body wt. 24 mo.	Animals with tumors at 20-24 months: Abdomen & Mammary	Pituitary	Others	TOTAL
CONTROL	M	35	25	19	10	3.47	1	0	1	2
	F	35	26	19	16	3.05	6	0	2	7
Aroclor 1242										
1 ppm	M	35	25	18	10	2.93	2	0	1	3
	F	35	28	24	10	3.00	10	2	2	11
10 ppm	M	35	25	20	12	3.18	2	1	1	3
	F	35	29	24	19	3.19	7	2	2	10
100 ppm	M	35	23	16	6	3.95	0	0	1	1
	F	35	27	19	10	4.82**	1	1	2	4
Aroclor 1254										
1 ppm	M	35	22	14	5	2.99	0	1	1	2
	F	35	29	24	21	3.10	11	1	2	11
10 ppm	M	35	26	18	8	3.21	0	0	2	2
	F	35	24	20	13	3.84*	6	2	2	9
100 ppm	M	35	24	17	8	4.75**	2	0	0	2
	F	35	22	18	12	8.62**	10	0	2	12
Aroclor 1260										
1 ppm	M	35	22	17	9	3.40	0	1	0	1
	F	35	27	21	16	3.35	5	3	1	6
10 ppm	M	35	20	12	6	2.87*	0	0	0	0
	F	35	26	21	18	3.19	5	3	3	8
100 ppm	M	35	22	16	6	4.67**	0	1	2	3
	F	35	23	16	12	4.42**	4	1	3	8

* $P < 0.05$, ** $P < 0.01$, significant difference from controls.

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Table D2. Liver pathology reported in Industrial Bio-Test Rat Experiment: Controls and animals fed 100 ppm PCBs.

	Controls		Aroclor 1242 100 ppm		Aroclor 1254 100 ppm		Aroclor 1260 100 ppm	
	M	F	M	F	M	F	M	F
REPORT OF NOVEMBER 1971 (ref. 207)								
Animals surviving 24 months	10	16	6	10	8	12	6	12
Animals with diagnoses reported at "final sacrifice":	11	14	6	14	11	15	10	15
Focal lymphoid infiltration	-	3	-	-	1	-	-	-
Focal degeneration	1	-	1	3	2	-	1	-
Necrosis	-	-	-	-	-	-	-	2
Vacuolar change (fatty)	-	-	3	11	3	10	2	3
Hypertrophy[a]	-	-	2	5	3	6	2	5
Hyperplasia[b]	2	2	0	3	3	3	-	6
Nodular hyperplasia	-	-	-	1	-	1	-	-
Hepatoma	-	-	-	-	-	1	-	-
Miscellaneous[c]	-	1	-	2	1	-	4	2
REPORT OF NOVEMBER 1975 (ref. 68)								
Animals with diagnoses reported at "24 month sacrifice":	-		20		27		27	
Nodular hyperplasia	-		8		13		7	
Hepatoma	-		2		4		5	
Cholangiohepatoma	-		1		2		2	

[a] Includes focal and centrolobular hypertrophy. [b] Includes ductile and focal hyperplasia. [c] Focal hepatitis 2; focal cholengiohepatitis 1; portal fibrosis 2, congestion 3, telangiectasis 1, chronic inflammation 1.

The vacuolar change was not seen in the control animals but was observed occasionally in livers from T-I (1 ppm) and T-II (10 ppm) animals. It was frequent in the T-III animals. This lesion is morphologically indicative of fatty degeneration. Formalin-frozen sections of livers from representative animals which displayed vacuolar changes were stained with Oil Red O to reveal the presence of fat. The vacuolar lesion in the cytoplasm of these cells was positively identified as fat.

The hypertrophic change found in the liver was focal and often limited to the central lobular area where groups of cells were swollen to two or three times their normal size with clear pink homogenous cytoplasm. The hyperplasia was associated with the same cells and appeared to be an extension of the hypertrophic lesion. The hyperplastic cells were also usually hypertrophic. The most severe examples of hyperplasia appeared as nodular growths with limited compression of the surrounding normal hepatic tissue.

The minor lesions of degeneration, hepatitis, ductule cell proliferation, necrosis and focal lymphoid infiltration seen in the control animals and the T-I and T-II groups are lesions of spontaneous disease and are not related to the Aroclor 1254. This level of liver disease is not unusual in rats of this age. (207, pp. 67-68.)

In 1975 the liver slides were re-examined by the original pathologist (416). Revised diagnoses are tabulated in Table D2A and summarised in the second part of Table D2 Although the 1975 report states that "in most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971" (416, p. 2), the diagnoses were in fact markedly different, including 11 hepatomas, 5 cholangio-hepatomas, and 28 examples of nodular hyperplasia in the animals treated with 100 ppm.

Table D2A. Liver pathology reported in Industrial Bio-Test rat experiment: 1975 re-diagnosis (ref. 416).

Dose rate (ppm):	Control	Aroclor 1242			Aroclor 1254			Aroclor 1260		
		1	10	100	1	10	100	1	10	100
No. of animals	23	31	30	20	31	26	27	25	23	27
Vacuolar change	1	7	8	9	8	10	13	5	6	10
Focal hypertrophy	0	2	3	8	3	5	13	3	10	11
Nodular hyperplasia	1	0	2	8	0	3	13	0	9	7
Hepatoma	0	0	0	2	0	0	4	0	0	5
Ductular hyperplasia	5	3	3	3	6	3	4	6	5	14
Cholangio-hepatoma	0	0	0	1	0	0	2	0	0	2
Hepatocellular necrosis	1	1	1	0	3	1	2	4	2	6

D.3 Apparent Conflict Between Results of Kimbrough and Industrial Bio-Test Experiments.

In presenting the revised results of the Industrial Bio-Test experiment, Calandra (68) suggested that they conflicted substantially with those of Kimbrough et al. Specifically, he emphasized that no hepatocellular carcinomas could be diagnosed in the Industrial Bio-Test experiment, that two consultants (in addition to the original pathologist) had reviewed the slides in 1975, and that one of these consultants had also reviewed slides from the Kimbrough, et al. experiment and "does not agree with the reported findings". However, this consultant also disagreed with the Industrial Bio-Test pathologists, reporting no tumors or even hyperplastic nodules in that experiment (417). In his review of the slides from the Kimbrough et al. experiment, this consultant diagnosed among 184 treated animals 136 hyperplastic nodules and 43 "hyperplastic nodules with atypical structures" (Table D2B). A review of this report suggests that the dispute is primarily over terminology, in particular over the severity of the criteria required for a diagnosis of neoplasia. This is an area in which the Agency has considerable expertise and has previously accepted the criteria and diagnoses of the principal pathologist* in the Kimbrough et al. study (270). Recognizing the terminological dispute, there does not seem to be substantial qualitative conflict between these two experiments. Even without the supporting evidence cited below, the two experiments together would justify a finding that Aroclor mixtures induce neoplastic transformations in rat livers.

* Dr. R. A. Squire, Head of the Tumor Pathology Section of the National Cancer Institute.

Nodular hyperplasia was also reported in 14 animals treated with 10 ppm and in one control. The tumors were described as follows:

> "Those lesions classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining, or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia, these are benign tumors rather than malignant tumors (carcinomas)." (416, p. 3)

There are substantial discrepancies between the total number of animals diagnosed and the numbers listed as surviving to 24 months in the original report (Table D2).

Comment. Although this experiment was continued for a full 24-month period and provides a useful comparison between the three Aroclors, the experimental groups were too small to provide a sensitive test for carcinogenicity. In particular, the use of only a single control group, reduced to 70 animals by interim sacrifices and to 26 by mortality in the second year, made the entire experiment very insensitive. The cause of the high mortality was not stated. The drastic changes in diagnoses between 1971 and 1975 were not explained and the tumors were inadequately described.

The 1975 report indicates that PCBs at 100 ppm in the diet induced a variety of proliferative lesions, including tumors and hyperplastic nodules, in the livers of exposed rats, and that these effects were induced at roughly similar frequency by each of the three Aroclors. No further conclusions can be drawn without a complete report and independent diagnoses of the lesions in the livers and pituitaries.

Table D2B (from raf. 417)

Differences of liver lesior in control and experimental rats treated with Aroclor 1260

	Experimentals	Controls
Vacuolization	155	13
Focal granular alteration	100	31
Single granular alteration	169	45
Single cell necrosis	125	17
Group cell necrosis	36	2
Cell enlargement	175	17
Ductal proliferation	52	3
Cholangiomatous lesion	7	-
Stern cell proliferation	121	87
Hyperplastic nodules:		
without atypia	136	9
with atypia	43	1

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