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Figure 4. Thin-layer radiochromatograms of urine samples of mice, which did not move in A solvent system and were rechromatographed in B solvent system.

lin-2-yl sulfenate and other metabolites of ETU is needed to clarify the toxicity of ETU.

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Fate and Effects of Pentachloronitrobenzene in Rhesus Monkeys

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Pure pentachloronitrobenzene (PCNB) was administered to rhesus monkeys as single oral doses of 0.5, 2, or 91 mg/kg bodyweight and in a 70-day feeding study at a level of 2 ppm in the daily diet. PCNB was readily absorbed from the gastrointestinal tract, metabolized, and excreted rapidly by both the urinary and the fecal route. Pentachloroaniline and pentachlorothioanisole were the major metabolites, accompanied by a variety of other biotransformation products containing nitrogen reduced to anilines and sulfur as thiophenols, thioanisoles, or sulfoxide. Feeding PCNB for 70 days did not result in significant accumulation of PCNB or its metabolites. Parameters of clinical chemistry, hematology, endocrinology, and histopathology remained within the limits of variation which are normal for rhesus monkeys.

Pentachloronitrobenzene (PCNB) is the active ingredient of a variety of fungicides, e.g., Quintozen, Terraclor, or Brassicol, used for seed and soil treatment in agriculture and horticulture. It can be produced by chlorination of nitrobenzene (Schlör, 1970) or by nitration of pentachlorobenzene (Häfner, 1976). The technical product may contain up to 6% of hexachlorobenzene (HCB) (Zimmerli and Marek, 1972; Stijve, 1971; Casanova and Dubroca, 1972), as well as pentachlorobenzene (QCB) and tetrachloronitrobenzenes (Beck and Hansen, 1974). In earlier studies, Kuchar et al. (1969) and Borzelleca et al. (1971) investigated the toxicokinetic behavior, biotransformation, and toxicological effects of PCNB in dogs, rats, and cows using Terraclor, which contained 1.8% of hexachlorobenzene, 0.1% pentachlorobenzene, and 0.4% 2,3,4,5-tetrachloronitrobenzene. Analyzing hexane extracts of feces, urine, organs, fat, and milk of the exposed animals, they found residues of hexa- and pentachlorobenzene as

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well as pentachloroaniline (PCA) and pentachlorothioanisole (PCTA). In view of the current knowledge of the toxicokinetic fate of HCB in mammals (Rozman et al., 1975, 1978) it may be assumed that the HCB residues reflect an accumulation of HCB from Terraclor, due to the extremely high storage tendency and slow biotransformation and excretion of this impurity. PCA and PCTA are metabolites of PCNB, while the residues of QCB could originate both from accumulation of the QCB impurity of Terraclor and from the biotransformations of PCNB or HCB. The fact that PCNB was not found in any of the tissues analyzed in those studies indicates a high rate of metabolic conversion and excretion of this compound.

Toxic effects of Terraclor in rats and dogs are essentially limited to liver enlargement due to hepatocellular hypertrophy (Finnegan et al., 1958; Borzelleca et al., 1971). As the commercial product used in these studies contained 1.8% HCB, the described hepatotoxicity may have been caused at least partially by HCB, especially in the chronic feeding studies, in which HCB was accumulated to a considerable extent. In cats, Borzelleca and co-workers found increased methemoglobin levels after moderate and high doses (Schuman and Borzelleca, 1978) of Terraclor. Feeding a very high dose (5000 ppm of the diet) of PCNB of undescribed purity to dogs for 2 years (FAO/WHO, 1970) resulted in reduced hematopoiesis. Again, the effect may have been caused by HCB, which was shown to accumulate in the bone marrow (Rozman et al., 1978). In order to investigate the biotransformation and the toxicokinetic behavior of pure PCNB in a species more closely related to man than rodents or dogs, we studied the uptake, body distribution, storage, metabolic conversion, and excretion of ^{14}C-labeled PCNB in rhesus monkeys, using low to moderate dose levels for single oral administration and a low dose for chronic feeding. While our primary objective was to study the fate of PCNB in the nonhuman primate under conditions similar to those of human environmental exposure, we also measured parameters of clinical chemistry, hematology, and endocrinology, looking for early indicators of PCNB toxicity. Complete autopsies and morphological tissue analyses were performed with all animals sacrificed during our studies.

MATERIALS AND METHODS

Pentachloronitrobenzene, purchased from ICN Pharmaceuticals Co., was purified by repeated column chromatography (silica gel/hexane). The final product contained <0.01% of chlorinated benzenes as determined by electron-capture gas chromatography. ^{14}C-labeled PCNB at a radiochemical purity of >99.9% (Sandrock et al., 1978) was obtained from the Institut für ökologische Chemie der Gesellschaft für Strahlen- und Umweltforschung mbH, Munich, Germany. Rhesus monkeys (*Macaca mulatta*) were obtained from the colony of the International Center of Environmental Safety. They were housed in stainless steel metabolism cages (Harford Metal) for the separate collection of urine and feces. The animals received a standard diet of Purina Monkey Chow, supplemented by fresh fruit, and 1 L of water per day. Residue analysis of the monkey chow showed that it contained <1 ppb of HCB and PCBs; no other pesticides could be detected.

The following individual experiments were carried out: (a) One female rhesus monkey was given 0.5 mg of PCNB/kg bodyweight (sp act., 4.3 mC/mM) in ethanol by stomach tube. Blood samples were taken in 30-min intervals for 3 h, then hourly until 7 h after dosing, then in 24-h intervals until day 5. Feces and urine were collected daily.

(b) Six male and two female monkeys were given a single oral dose of 2 mg of PCNB/kg bodyweight each (sp act., 0.7 mC/mM), suspended in 1% aqueous methyl cellulose solution by gastric intubation. Two males were sacrificed after 24 and 48 h, respectively, and complete autopsies were performed with both animals. Feces and urine of the other monkeys were collected daily for 14 days.

(c) One female rhesus monkey received 91 mg of PCNB/kg bodyweight (sp act., 0.08 mC/mM) in sesame oil by stomach tube, feces and urine were collected daily for 20 days. Blood samples were taken on days, 1, 2, 8, 10, 16, 18, 21, and 23 after dosing.

(d) Two male and two female rhesus monkeys were given 70 consecutive daily doses of PCNB on sucrose pellets corresponding to 2 ppm of their daily diet (sp act., 0.8 mC/mM). Feces and urine were collected daily, blood samples were taken on day 5, then biweekly. One male and one female monkey were sacrificed on the day after the last dose for complete autopsy, the excreta of the remaining two animals were collected until day 80 without further administration of PCNB.

The total radioactivity in urine and in extracts was measured by direct liquid scintillation counting, using Tri-Carb 2425 (Packard Instrument Co.) counters and a dioxane cocktail which contained 8 g/L of Permablend III (Packard), 10% v/v of methanol, and 10% w/v of naphthalene. For the determination of radioactivity in feces, tissues, plasma, or red blood cells, triplicate aliquot samples of ca. 200 mg each were combusted in an automatic sample oxidizer (Packard Tri-Carb 306) in which Carbosorb (Packard) was used as ^{14}CO$_2$ absorber and Permafluor (Packard) as scintillation cocktail. External standardization was used for quench correction with all samples.

To isolate and purify the radioactive material in the excreta, the urine was acidified to pH 2 with sulfuric acid and extracted with ethyl ether in liquid–liquid extractors for 24 h. Feces were mixed thoroughly with equal amounts of anhydrous sodium sulfate and extracted with methanol in Soxhlet extractors for 24 h. The extracts were purified by column chromatography on silica gel using benzene/chloroform (1:1, v/v), chloroform, acetonitrile, and methanol as solvents. The column fractions containing radioactivity were further purified by preparative thin-layer chromatography on silical gel plates with hexane or hexane/acetone (9:1, v/v) as solvents. After localization and quantitation of the radioactive zones by means of radio-TLC-scanners (Berthold), the zones were removed from the plates and washed with methanol, and the concentrated eluates were analyzed by gas chromatograpy–mass spectrometry, using a Finnigan 3000 D system. GC–MS conditions were as follows: column, 5 ft × 2 mm i.d. borosilicate glass; stationary phase, 3% OV-1 on Supelcoport (80–100 mesh); carrier gas, 20 mL/min helium; column temperature, 160–210 °C, 5 °C/min; injector temperature, 220 °C; separator, single-stage glass jet, 230 °C; ion source, electron impact 70 eV, 130 °C. Blood samples collected in experiments c and d were examined for hematological changes. The contents of hemoglobin and methemoglobin were measured according to Miale (1972) and Tietz (1976). For the hematocrit determination a microhematocrit centrifuge (International) was used, and white and red blood cells were counted in a Coulter counter (Coulter Diagnostics).

In the blood samples from the 70-day feeding study, parameters of clinical chemistry and endocrinology were monitored. Sodium and potassium were measured by flame photometry (Instrumentation Laboratory Inc.), using lithium as internal standard. Bilirubin, creatinine, blood

Table I. Concentration of PCNB and/or Metabolites (ppm, Mean ± SD) in Tissues of Male Rhesus Monkeys 24 and 48 h after a Single Oral Dose of 2 mg/kg Bodyweight

organ/tissue	24 h	48 h
liver	2.3 ± 0.1	0.5 ± 0.01
bile	275.9 ± 0.3	14.4 ± 0.4
kidney	1.6 ± 0.04	0.4 ± 0.07
adrenal cortex	0.4 ± 0.03	0.2 ± 0.01
thymus	0.7 ± 0.03	0.4 ± 0.09
bone marrow	0.5 ± 0.05	0.4 ± 0.07
heart	0.1 ± 0.03	<0.1
muscle	0.2 ± 0.04	<0.1
lymph nodes[a]	0.3 ± 0.1	0.4 ± 0.2
fat[a]	0.3 ± 0.2	0.6 ± 0.1
brain[a]	0.1 ± 0.02	<0.1
blood		
plasma	0.4 ± 0.04	0.2 ± 0.06
RBC	0.3 ± 0.01	0.1 ± 0.04

[a] Average of several sampling sites.

Table II. Tissue Concentrations of PCNB and/or Metabolites (ppm, Mean ± SD) in Rhesus Monkeys after Feeding 2 ppm of PCNB for 70 Days

organ/tissue	male	female
liver	0.19 ± 0.01	0.15 ± 0.01
bile	7.73 ± 0.2	3.72 ± 0.05
kidney	0.14 ± 0.01	0.1 ± 0.01
adrenal cortex	0.08 ± 0.04	0.05 ± 0.01
thymus	0.19 ± 0.01	0.17 ± 0.03
bone marrow	0.13 ± 0.01	0.16 ± 0.02
heart	0.02 ± 0.005	0.01 ± 0.005
lung	0.04 ± 0.008	0.04 ± 0.004
muscle	0.01 ± 0.005	0.02 ± 0.01
lymph nodes[a]	0.06 ± 0.02	0.06 ± 0.05
fat[a]	0.19 ± 0.02	0.1 ± 0.02
brain[a]	0.03 ± 0.01	0.02 ± 0.004
blood		
plasma	0.07 ± 0.02	0.05 ± 0.01
RBC	0.03 ± 0.01	0.01 ± 0.004

[a] Average of several sampling sites.

urea nitrogen (BUN), total proteins, serum glutamate-oxaloacetate–transaminase (SGOT), serum glutamate-pyruvate–transaminase (SGPT), lactate dehydrogenase (LDH), and cholesterol were determined in a Centrifichem Parallel Analyzer (Union Carbide). Luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured by radioimmunoassay according to Faiman et al. (1975) and progesterone according to Reyes et al. (1975). For the cortisol determination, a radioimmunoassay kit of Micromedic Diagnostics Inc. was used.

RESULTS AND DISCUSSION

A detailed description of the toxicokinetic behavior and the biotransformation of PCNB in our studies with rhesus monkeys has been given elsewhere (Kögel et al., 1979a,b). Essentially our findings were as follows. PCNB is readily absorbed from the gastrointestinal tract, the radioactivity level in plasma after a single oral dose of 0.5 mg of PCNB-^{14}C/kg bodyweight reached a maximum after 1.5 h. A second maximum after 5 h is probably caused by the rapid formation of metabolites which start building up in the circulating blood a few hours after administration.

The uptake occurs mainly by the portal venous route, with little involvement of the lymphatic system. This brings the absorbed PCNB directly to the liver, where the biotransformation can start immediately.

After a single oral dose of 2 mg/kg, given in methyl cellulose suspension, only 7.4% of the administered amount was excreted as unmetabolized PCNB in the feces, indicating almost complete absorption. An even higher absorption rate was found when 91 mg/kg of PCNB was given in sesame oil; only 4.3% of the dose was excreted unmetabolized.

Twenty-four hours after single oral dose of 2 mg/kg, the males excreted 27.5% of the dose in urine and 10% in feces, while the females excreted 22.1% in urine and 20.4% in feces. The total excretion by the males after 14 days was 84.8% of the dose (38.5% in urine and 46.3% in feces), and 81.0% (36.2% in urine and 44.8% in feces) by the females.

Excretion after single oral dose of 91 mg/kg was somewhat slower and less complete: after 24 h, only 15.1% of the dose was excreted (urine, 11.8%; feces, 3.3%), and after 20 days, the total excretion was 59.5% (25.8 in urine and 33.7% in feces).

Tissue analysis of the two monkeys sacrificed 24 and 48 h, respectively, after single oral dose of 2 ppm revealed a high concentration of radioactive material only in the bile (Table I). Liver and kidney contained moderate amounts of radioactivity, whereas the concentrations in fat, thymus,

bone marrow, adrenal cortex, and lymph nodes were only slightly higher than in the rest of the tissues.

Feeding PCNB-^{14}C for 70 days at a dose level corresponding to 2 ppm of the daily diet did not result in significant accumulation of radioactive material. A plateau level of storage was reached after 30–40 days, indicated by an equilibrium of uptake and excretion. On day 71, the males had retained 7.7%, the females 10.3% of the total dose. The body distribution in a male and a female sacrificed on day 71 is given in Table II. Ten days after the last administration, the surviving male monkey had excreted 96.4% and the female 94.3% of the total dose.

PCNB is rapidly metabolized to a variety of biotransformation products. Two major pathways were found to be utilized in the rhesus: reduction of the nitro moiety to the corresponding aniline and conjugation with sulfur-containing peptides, e.g., glutathione, resulting in highly polar metabolites which are excreted in the bile. Secondary cleavage reactions with these conjugates produce thiophenols and thioanisoles and probably also pentachlorobenzene and pentachlorophenol, which were identified as metabolites.

Major metabolites found in all individual experiments were pentachloroaniline, pentachlorophenol, pentachlorothioanisole, and pentachlorobenzene, as well as a dimethylmercaptotetrachlorobenzene. Pentachlorothiophenol, 2,3,4,5-tetrachloroaniline, and a tetrachloroaminothioanisole were found in smaller quantities after both low- and high-dose single oral administration and during the feeding study. The metabolites found only after a single oral dose of 91 mg/kg include 2,3,5,6-tetrachlorophenol, tetrachlorothioanisole, tetrachloroaminophenyl methyl sulfoxide, and dimethylmercaptoaminotrichlorobenzene.

The parameters of hematology in the female rhesus which was given 91 mg of PCNB/kg bodyweight are listed in Table III. The values for hemoglobin (Hgb), packed cell colume (PCV), red blood cells (RBC), and white blood cells (WBC) show no dose-related effect. The level of methemoglobin (Mgb) was somewhat elevated on day 1 after dosing and returned to the normal level on the following day. No increase in the number of erythrocytes with Heinz bodies was noted.

During the 70-day feeding study, all measured hematology parameters remained within normal limits (Table IV).

In blood samples taken before the first dose, on days 19 and 48 of the 70-day feeding study, and on day 76 from the two animals which were not sacrificed, parameters of

Table III. Parameters of Hematology in a Female Rhesus Monkey after Administration of 91 mg/kg of PCNB

day	Hgb, g/100 mL	PCV, vol %	RBC/mm³ × 10⁶	WBC × 10³	Mgb, mg/100 mL
0[a]	15.6	48	6.15	10.4	67
1	14.1	44	6.01	6.5	302
2	15.4	44	6.04	16.9	100
8	14.9	45	6.19	8.0	67
15	14.1	43	4.87	8.7	100
16	15.4	42	5.34	10.7	67
normal[b]	14.3 ± 1.3	43.5 ± 3.5	5.5 ± 0.6	13.1 ± 4.0	0.5–1.5% of total Hgb
2 CV (%)[c]	6.67	8.71	7.14	5.64	

[a] Preexposure control.   [b] Normal values, derived from a large number of control measurements accumulated during various rhesus toxicology studies at ICES.   [c] Coefficient of variance of measurement procedure.

Table IV. Parameters of Hematology during and after Chronic Feeding of 2 ppm PCNB in the Daily Diet[a]

day	sex	Hgb, g/100 mL	PCV, vol %	RBC/mm³ × 10⁶	WBC × 10³
0[b]	M	15.45 ± 0.35	46.5 ± 2.12	5.69 ± 0.2	10.15 ± 0.92
19	M	14.3 ± 1.13	44.0 ± 5.6	5.545 ± 0.672	10.25 ± 4.45
48	M	15.35 ± 0.92	48.5 ± 2.12	6.245 ± 0.39	9.7 ± 0.14
76	M	15.6	49	6.7	7.7
0[b]	F	15.9 ± 0.28	49.0 ± 1.4	5.96 ± 0.18	8.8 ± 2.83
19	F	14.9 ± 0.28	46.5 ± 0.71	5.975 ± 0.06	7.8 ± 0.85
48	F	14.0 ± 0.56	44.0 ± 2.8	6.03 ± 0.68	4.1 ± 5.8
76	F	14.8	47	6.76	10.5

[a] For normal values cf. Table III.   [b] Preexposure control.

Table V. Parameters of Clinical Chemistry in Rhesus Monkeys during 70-Day Feeding Study

	normal[a]	sex	days 0[b]	days 19	days 48	days 76
total protein, g/dL	7.56 ± 0.76	M	7.4 ± 0.56	6.45 ± 0.64	8.25 ± 0.21	7.2
	7.42 ± 0.62	F	7.8 ± 0.42	8.0 ± 0.28	8.1 ± 0.71	7.0
albumin, g/dL	4.15 ± 0.75	M	4.5	3.9 ± 0.14	4.5 ± 0.28	5.3
	4.15 ± 0.75	F	4.45 ± 0.07	4.15 ± 0.21	4.05 ± 0.21	4.9
cholesterol	169 ± 35	M	128 ± 14	188 ± 16.9	183.5 ± 7.77	200
	168 ± 41	F	247.5 ± 48.8	282	264 ± 19.8	280
SGOT, U/L	22 ± 4	M	24 ± 7.07	23.5 ± 0.71	23.5 ± 6.4	69
	21 ± 4	F	24.5 ± 2.1	31 ± 11.3	17.5 ± 4.9	41
SGPT, U/L	19 ± 4	M	28 ± 9.9	6.5 ± 9.2	23.5 ± 7.8	26
	18 ± 5	F	23 ± 7.1	21 ± 8.5	18 ± 2.8	21
LDH	219 ± 89	M	318.5 ± 239.7	427.5 ± 16.3	295.5 ± 188.8	442
	226 ± 88	F	316.5 ± 84.1	386.5 ± 153	132 ± 42.4	228
Na, mequiv/L	152 ± 5	M	150.5 ± 0.71	151 ± 2.83	150 ± 2.83	148
	150 ± 5	F	148 ± 1.4	151.5 ± 2.1	147	151
K, mequiv/L	4.79 ± 0.68	M	4.55 ± 0.64	4.6 ± 0.42	4.55 ± 0.35	4.5
	4.51 ± 0.58	F	4.2 ± 0.42	5.35 ± 0.64	4.0 ± 0.14	4.2
Ca, mequiv/L	5.06 ± 0.44	M	5.0	4.3 ± 0.14	5.2 ± 0.28	4.8
	5.16 ± 0.36	F	4.85 ± 0.07	4.25 ± 0.07	4.8 ± 0.14	5.0
bilirubin, mg/dL	0.25 ± 0.21	M	0.235 ± 0.26	0.41 ± 0.14	0.12	0.18
	0.20 ± 0.15	F	1.15 ± 0.04	1.34 ± 1.02	0.06	0.1
creatinine, mg/dL	1.52 ± 0.46	M	1.6 ± 0.14	1.5	2.0 ± 0.28	1.7
	1.22 ± 0.26	F	0.8 ± 0.04	0.62 ± 0.31	1.5	1.3
BUN, mg/dL	25 ± 7	M	22.5 ± 2.12	19	27	24
	23 ± 6	F	18.5 ± 0.71	17.5 ± 0.71	24 ± 2.8	31

[a] Normal values, derived from a large number of control measurements accumulated during various rhesus toxicology studies at ICES.   [b] Preexposure control.

Table VI. Serum Cortisol Levels (ng/mL) in Rhesus Monkeys before, during, and after Feeding of 2 ppm PCNB in the Diet for 70 Days

day	male	female
preexposure control	174.2 ± 38.6	164.9 ± 50.9
	222.1 ± 73.9	300.7 ± 18.6
	202.3 ± 107.7	407.1 ± 20.7
14	219.3 ± 72.3	276.9 ± 3.8
28	239.4 ± 93.5	342.5 ± 20.2
42	278.5 ± 7.4	372.7 ± 40.1
56	258.2 ± 1.7	394.5 ± 109.7
70	241.6 ± 63.2	496.5 ± 72.0
84	168.1	269.8
133	224.2	241.5
161	283.6	530.7
175	335.7	525.7

clinical chemistry were measured (Table V). The values for total proteins, albumin, and cholesterol in serum remained within the normal variance of the preexposure control measurement. Likewise, the electrolytes (sodium, potassium), calcium, and the enzymes SGOT, SGPT, and LDH remained within normal limits, and so did the values of creatinine and blood urea nitrogen (BUN). The bilirubin measurements varied widely (between 0.05 and 2.06 mg/dL), but no dose-related effect of PCNB could be seen.

In studies with other chlorinated compounds like dieldrin (Müller et al., 1975; Rozman et al., 1978), the adrenal cortex of the rhesus monkey had been found to accumulate the chemicals to relatively high concentrations. As this organ is the site of corticosteroid production, it is

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possible that the chemicals accumulating in its cells interfere with the synthesis or release of these important hormones. Looking for a potential effect of PCNB on the function of the adrenal cortex, cortisol levels were measured in the animals used for the 70-day feeding study. Blood samples were taken before, during, and after the feeding period and analyzed for their cortisol content by radioimmunoassay. The results listed in Table VI show that no effect of PCNB on the level of cortisol in the circulating blood could be seen. In the same blood samples, the radioimmunoassays for luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone did not show any gross effects of PCNB on the levels of these hormones in circulating blood. It must be pointed out, however, that this experiment was not designed as an endocrinology study and that more subtle interferences of PCNB with hormone patterns may have remained undetected.

Samples of liver, stomach, small and large intestine, spleen, kidneys, heart, lung, thymus, cerebrum, cerebellum, pons, medulla, spinal cord, and bone marrow were taken for histological examination from the male monkeys sacrificed 24 and 48 h after a single oral dose of 2 mg of PCNB/kg bodyweight, as well as of one male and one female sacrificed on day 71 of the feeding study. All morphological findings were within limits of variation which are normal in rhesus monkeys.

CONCLUSION

In the rhesus monkey, pentachloronitrobenzene is readily absorbed from the gastrointestinal tract, primarily by the portal venous route. It is rapidly converted to pentachloroaniline and a variety of other metabolites, many of which contain sulfur, indicating that glutathione conjugation plays a major role in its biotransformation, although introduction of the *S*-methyl moiety by way of methionine cannot be excluded on the basis of our findings. The high rate of nitro reduction together with the multitude of polar metabolites formed from PCNB results in its rapid excretion by both the renal and the biliary route, with a half-life of 1.5–1.7 days after low doses. The elimination rate is remarkably higher than that of other highly chlorinated chemicals; pentachlorophenol, which is comparable to pentachloroaniline in its polarity, has a half-life of 15–20 days in rhesus monkeys after single oral dose (Ballhorn, 1978). As a consequence of its fast elimination, PCNB has virtually no accumulation tendency; the amounts of radioactive material found in the organs and tissues of monkeys after an intake of 2 ppm of PCNB in their diet for 70 days were very low. Unchanged parameters of clinical chemistry and hematology throughout the feeding study indicate that organ function and hematopoiesis was not affected by PCNB or its metabolites. A slight elevation of the methemoglobin level in blood was only found 24 h after administration of a moderately high dose (91 mg/kg).

On the basis of the findings with rhesus monkeys it may be suggested that PCNB is not likely to accumulate in humans who take up small amounts of it through food or other environmental or even mild occupational exposure. Under conditions of continued low-level intake neither the parent compound nor any of its metabolites has to be expected to build up in target tissues to potentially dangerous concentrations.

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