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Urinary excretion of chlorinated phenols in saw-mill workers

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Summary. The excretion and conjugation of chlorophenols were studied in workers exposed to 2,4,6-tri-, 2,3,4,6-tetra-, and pentachlorophenolates, the main components of the chlorophenolate product manufactured by direct chlorination of phenol. The workers were exposed in two different saw mills in which sodium chlorophenolate was used for treatment of lumber during the warm season. Urine specimens were collected at the end of the treatment season as well as at the start of a new treatment period in the spring. Serum specimens were collected towards the end of the treatment period. Total and unconjugated chlorophenols were analyzed with a gas chromatographic method. The maximal concentrations of urinary 2,4,6-tri-, 2,3,4,6-tetra- and pentachlorophenol at the end of the lumber-treatment period were 1–11.8, 3.4–17.3, and 0.2–0.9 μmol/l, respectively, and the average apparent half-times calculated using a one-compartment model were 18 h, 4.3 days and 16 days, respectively. For 2,3,4,6-tetrachlorophenol, the data of some subjects showed a better fit with a two-compartment model; the corresponding half-times were 5.3 and 26 days. During the continuous-exposure period the average serum levels of tetra- and pentachlorophenol were rather similar before and after the working day: 2.79 ± 1.78 μmol/l for tetrachlorophenol and 0.85 ± 0.4 μmol/l for pentachlorophenol. Renal clearance values for tetra- and pentachlorophenol were related to urine flow and indicated tubular reabsorption. At low concentrations, sulfate conjugation was dominant. With increasing chlorophenol concentrations the proportion of glucuronide conjugation was increased, especially for pentachlorophenol.

Key words: Chlorophenols – Excretion – Conjugation – Half-times – Renal clearance

Introduction

Chlorophenol products have been widely used for treatment of lumber after sawing so as to prevent fungal growth. The possible carcinogenicity of chlorophenols to man, IARC classification 2B [12], has raised concern about the exposure of workers to these compounds. As the chlorophenols are absorbed readily through the skin, hygienic ambient air measurements do not necessarily reveal the total amount absorbed into the body; hence, urine specimens have been increasingly used in monitoring the exposure of workers [4, 7, 13, 15, 17, 19, 20, 24]. Urinary excretion of chlorophenols has also been analyzed by Angerer et al. [3] as a measure of exposure to hexachlorobenzene. In animal studies the clearance rates vary from one chlorophenol compound to another and depend on the extent of chlorination [1, 5, 21, 22]. To determine the optimal timing of specimen collection for the biological monitoring of chlorophenol exposure, we studied the rates of excretion of the main components of the chlorophenolates used for lumber treatment.

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Subjects and methods

Specimen collection. The study group comprised seven workers (one woman and six men) in two saw mills in which a sodium chlorophenolate product (KY 5, Kymi Ltd, Kuusankoski, Finland) was used for treatment of lumber. The workers in sawmill I were exposed when moving lumber, freshly sawn and wet from having been dipped in the chlorophenol solution, from the conveyor belt to the drying area. The treatment of lumber starts in April or May and ends in October or November. Urine and blood (serum) specimens were collected at three time points:

1. During the continuous treatment period, blood specimens were drawn before and after the working hours on the 4th day (Thursday) of a working week. On the same day, all voided urine (24 h) was collected in five portions starting in the morning. Spot urine specimens were also collected in the mornings of the 2 subsequent days (Friday and Saturday) and at the end of the following week on Friday and Saturday as well.
2. Urine specimens were also collected on the mornings of the 1st, 2nd, 3rd, 5th, 10th, 20th, 40th, and 171st days after the end of the treatment season for the year.
3. Finally, when lumber treatment was restarted in the spring, urine specimens were collected before and after working hours during the 1st week and before the work day during the 2nd week.

For the calculation of half-times, morning specimens were also collected also from two workers in sawmill II. Specimen collection

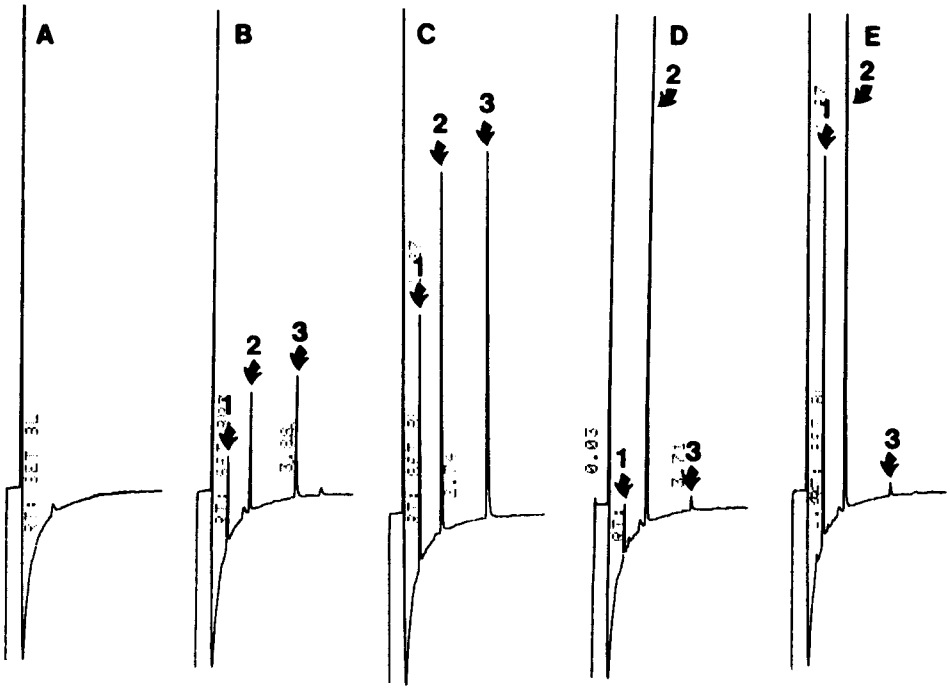

Fig. 1. Gas chromatographic separation of 2,4,6-tri-, 2,3,4,6-tetra-, and pentachlorophenols. *A*, Control urine; *B, C*, additions of tri-, tetra-, and pentachlorophenols in urine ($B = 1.62$, 0.87, and 0.75 µmol/l; $C = 4.06$, 2.6, and 2.25 µmol/l, respectively); *D, E*, urine of exposed workers

was carried out from Thursday until Monday. To measure the extent and type of conjugation, 21 samples collected for routine biological monitoring measurements were analyzed.

Analysis of the dipping solution. The chlorophenol content of the dipping solution in sawmill I was analyzed by liquid chromatography [20] using all possible chlorophenol isomers (Fluka AG), except 2,4,5-trichlorophenol as reference compounds.

Urine and serum analyses. The total and unconjugated 2,4,6,tri-, 2,3,4,6-tetra-, and pentachlorophenols were analyzed in urine, but only total chlorophenols were determined in serum. Determinations were based on gas chromatographic and liquid chromatographic methods used for biological monitoring of chlorophenols in Finland [20–22]. Extraction of chlorophenols was carried out under acidic conditions and purification was done with back-extraction to basic borate buffer. Reextraction was performed to an organic phase containing the acetylation reagent. Thus, evaporation steps [2, 3] before the derivation could be avoided.

In the analysis of total chlorophenols, complete hydrolysis of all conjugates was ensured by using hydrochloric acid. In brief, 1 ml of 6 mol/l hydrochloric acid and 2 ml of sample were boiled in stoppered tubes in a water bath for 15 min. After cooling, chlorophenols were extracted with 10 ml of *n*-hexane-isopropanol (5 + 1) by mixing for 10 min in a mechanical shaker. After centrifugation, an aliquot of 5 ml was taken from the organic phase and extracted with 4 ml of 0.1 mol/l sodium tetraborate in water. Then, 3 ml of the sodium tetraborate phase was combined with 10 ml of *n*-hexane containing 50 µl of a mixture of acetic acid anhydride and pyridine (2 + 5). Complete acetylation was ensured by thorough shaking for 15 min. Standards were prepared in urine and serum and treated like samples.

For gas chromatography, 1–5 µl of acetylated chlorophenols in hexane was injected into a Hewlett Packard gas chromatograph 5730 equipped with a ^{63}Ni electron-capture detector. Separation was done on an OV-101 methyl silicone fluid capillary column measuring 12 m in length × 0.21 mm in inside diameter (Fig. 1). The nitrogen flow rate was 1 ml/min, the temperature of the injector and detector was 300°C, and the column temperature was 150°C.

Quantification was achieved using peak heights in the linear concentration area. The limit of detection of the method was 0.05 µmol/l for all three chlorophenols, and the coefficients of variation are shown in Table 1. As an internal quality control, pooled urine from exposed workers that had been stored frozen was analyzed within each series.

Unconjugated chlorophenols. The determination of unconjugated chlorophenols was done by adjusting the urine to pH 2 using hydrochloric acid and a pH-meter, but the extraction procedure was continued without hydrolysis. The standards were treated like samples. The extent of conjugation was calculated based on the difference between total and unconjugated chlorophenol concentrations [21].

Table 1. Coefficients of variation calculated from double determinations of 2,4,6-tri-, 2,3,4,6-tetra-, and pentachlorophenols

Compound	Number of duplicates	Concentration range (µmol/l)	CV	Concentration range (µmol/l)	CV	Concentration range (µmol/l)	CV
TriCP	10	< 0.1	0.11	≥ 0.1–1.5	0.07	≥ 1.5	0.04
TCP	10	< 0.5	0.09	≥ 0.5–2	0.02	≥ 2	0.02
PCP	10	< 0.2	0.17	≥ 0.2–1	0.03		

TriCP, 2,4,6-trichlorophenol; TCP, 2,3,4,6-tetrachlorophenol; PCP, pentachlorophenol

Type of conjugation. To assess the type of conjugation, enzymatic hydrolysis was used. In brief, 1 ml of a sample was mixed with sodium acetate buffer (0.1 mol/l) to adjust the pH to 5 and was then treated for 17 h at 37°C with 100 µl (9,790 IU) β-glucuronidase containing aryl sulfatase (Sigma number G-0876 from *Helix pomatia*, USA). The same procedure was repeated with 0.5 mmol/l D-glucaro-1,4-lactone (Sigma number S-0375, USA) as an inhibitor.

Renal clearance. The renal clearance of 2,3,4,6-tetra- and pentachlorophenol during the first specimen collection in sawmill I was calculated from determinations of total chlorophenols in serum and urine. The clearance values for 2,4-6-trichlorophenol could not be determined due to fluctuating levels in the serum.

Elimination and half-times. The elimination of trichlorophenol in the workers of both mills was calculated using a one-compartment model from the concentrations on days 1–3 or 1–5. The elimination of tetrachlorophenol in three of the five workers in mill I showed a better fit to a two-compartment model; thus, two consecutive elimination rate constants were calculated for days 2–5 and 10–40. In two workers in both mills the elimination of tetrachlorophenol closely followed a single exponential pattern; the half-times were calculated from the concentrations on days 2–5 or 1–10. The rates of elimination of pentachlorophenol were calculated for five workers in mill I based on the one-compartment model (days 1–40), whereas the concentrations of pentachlorophenol in sawmill II were too low for accurate kinetic calculations.

Table 2. Chlorophenol concentrations in serum before and after working hours during continuous exposure

Person code	a.m./p.m.	S-TriCP (µmol/l)	S-TCP (µmol/l)	S-PCP (µmol/l)
1	a.m.	ND	1.12	0.25
	p.m.	ND	1.05	0.26
2	a.m.	0.03	1.84	0.72
	p.m.	0.10	1.92	0.81
3	a.m.	0.26	6.05	1.44
	p.m.	0.53	6.01	1.49
4	a.m.	0.46	3.35	1.00
	p.m.	0.23	3.22	0.95
5	a.m.	0.13	1.60	0.76
	p.m.	0.23	1.68	0.74
Mean	a.m.	0.18	2.79	0.84
SD	a.m.	0.17	1.79	0.39
Mean	p.m.	0.22	2.78	0.85
SD	p.m.	0.17	1.76	0.40

a.m., Before working hours; p.m., after working hours; ND, not detected; S-TriCP, serum 2,4,6-trichlorophenol; S-TCP, serum 2,3,4,6-tetrachlorophenol; S-PCP, serum pentachlorophenol

Results

The chlorophenols found in the dipping solution were 2,4,6-tri-, 2,3,4,6-tetra, and pentachlorophenol. The quantitative analysis of the dipping solution revealed that the total chlorophenol content comprised 23% tri-, 74% tetra-, and 3% pentachlorophenol. The composition is thus approximately similar to that published for the Finnish product used in other sawmills [16].

The concentrations of chlorophenols determined in serum before and after working hours during the continuous-exposure period are shown in Table 2. On average, 2,4,6-tri-, 2,3,4,6-tetra-, and pentachlorophenol constituted 4%, 73%, and 23%, respectively, of the total chlorophenols in the specimen taken in the morning. A very similar average distribution was observed after working hours. The serum levels of trichlorophenol fluctuated markedly during the working day, whereas those of tetra- and pentachlorophenol were rather stable.

The maximal concentrations of chlorophenols after the period of exposure were between 1 and 11.8 µmol/l for trichlorophenol, 3.4–17.3 µmol/l for tetrachlorophenol, and 0.2–0.9 µmol/l for pentachlorophenol in the urine of the different workers. The decrease in the concentration of chlorophenols in the urine was not smooth; high values were detected on days 5 (Wednesday) and 20 (Thursday) (Fig. 2). There was some chlorophenol even in specimens collected at > 5 months after the treatment. After the dipping process had been restarted in the spring, the urinary chlorophenol concentration reached a plateau within 1 week.

The elimination rate constants determined using the one-compartment model were $0.04 \pm 0.010\,h^{-1}$, $0.24 \pm 0.16\ day^{-1}$ and $0.044 \pm 0.018\ day^{-1}$ for tri- tetra-, and pentachlorophenol, respectively, and the corresponding half-times were 18 h, 4.2 days and 16 days, respectively.

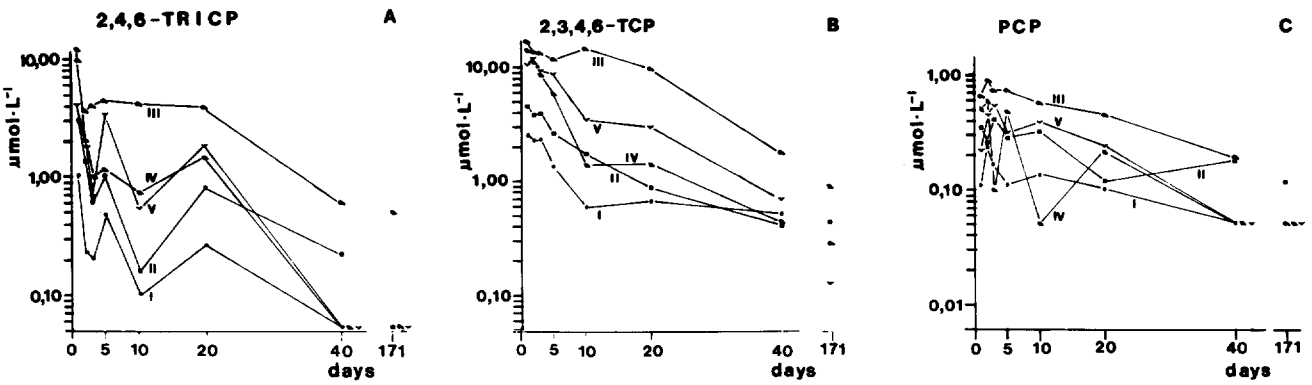

Fig. 2A–C. Concentrations of **A** tri- (*2,4,6-TRICP*), **B** tetra- (*2, 3, 4, 6-TCP*), and **C** pentachlorophenol (*PCP*) in urine of exposed workers in the morning after the end of the yearly timber-treatment period

Table 3. Concentrations and extent of conjugation of chlorophenols in urine during lumber treatment and during the 1st week after the start of a new treatment period in sawmill I

	2,4,6-TriCP Mean ± SD	2,3,4,6-TCP Mean ± SD	PCP Mean ± SD
A. All			
Concentration (μmol/l)	5.04 ± 7.07	7.59 ± 6.74	0.34 ± 0.24
Conjugation (%)	97.9 ± 2.6	92.9 ± 4	76.2 ± 14.2
B. Morning			
Concentration (μmol/l)	1.41 ± 1.33	2.47 ± 1.77	0.06 ± 0.04
Conjugation (%)	80.5 ± 29.3	79.1 ± 3.2	69.1 ± 27.1
B. Afternoon			
Concentration (μmol/l)	2.19 ± 3.2	32.87 ± 2.95	0.06 ± 0.03
Conjugation (%)	86.4 ± 23.1	81.6 ± 24.6	69.2 ± 28.7

A, during lumber treatment; B, during the 1st week after the start of a new treatment period; 2,4,6-TriCP, 2,4,6-trichlorophenol; 2,3,4,6-TCP, 2,3,4,6-tetrachlorophenol; PCP, pentachlorophenol

The two-compartment analysis of the elimination of tetrachlorophenol gave 0.14 ± 0.035 day^{-1} as the first and 0.037 ± 0.022 day^{-1} as the second elimination rate constant; the half-times were 4.3 and 26 days.

The tri- and tetrachlorophenols in urine were almost totally conjugated. The extent of conjugation of pentachlorophenol in urine was lower (Table 3). Almost complete hydrolysis of tri-, tetra-, and pentachlorphenols was achieved using β-glucuronidase-arylsulfatase treatment as compared with acid hydrolysis. Specific inhibition of β-glucuronidase did not decrease the yield of the different chlorophenols in the hydrolysis (Table 4).

Figure 3 shows the renal clearance of tetra- and pentachlorophenol as a function of the urinary excretion rate. The clearance values increased in relation to the urinary flow; minimal clearances were 1.1 and 0.2 ml/min for tetra- and pentachlorophenol, respectively.

Discussion

Jones and co-workers [13] reported urinary levels of pentachlorophenol amounting to 5–1,260 nmol/mol creatinine in persons working with wood preservatives, which are on the same order of the levels we observed during the treatment period in sawmill I (Table 4).

Elevated chlorophenol concentrations were also detected in the urine of sawmill workers during the working week long after the yearly lumber treatment was finished (Fig. 2). Especially in the concentration of trichlorophenol, with a short half-time in urine, one could easily see work-related changes in the chlorophenol excretion in urine. After the first morning of specimen collection (Friday) there was a decrease in trichlorophenol concentration that lasted until the weekend was over. The 5th (Wednesday) and 20th (Thursday) days showed an increase in urinary chlorophenol concentration, whereas the 10th (Monday morning) day showed the decreasing effect of absence from work. These variations are probably caused by chlorophenol contamination in the workplace. It has previously been shown that rather high

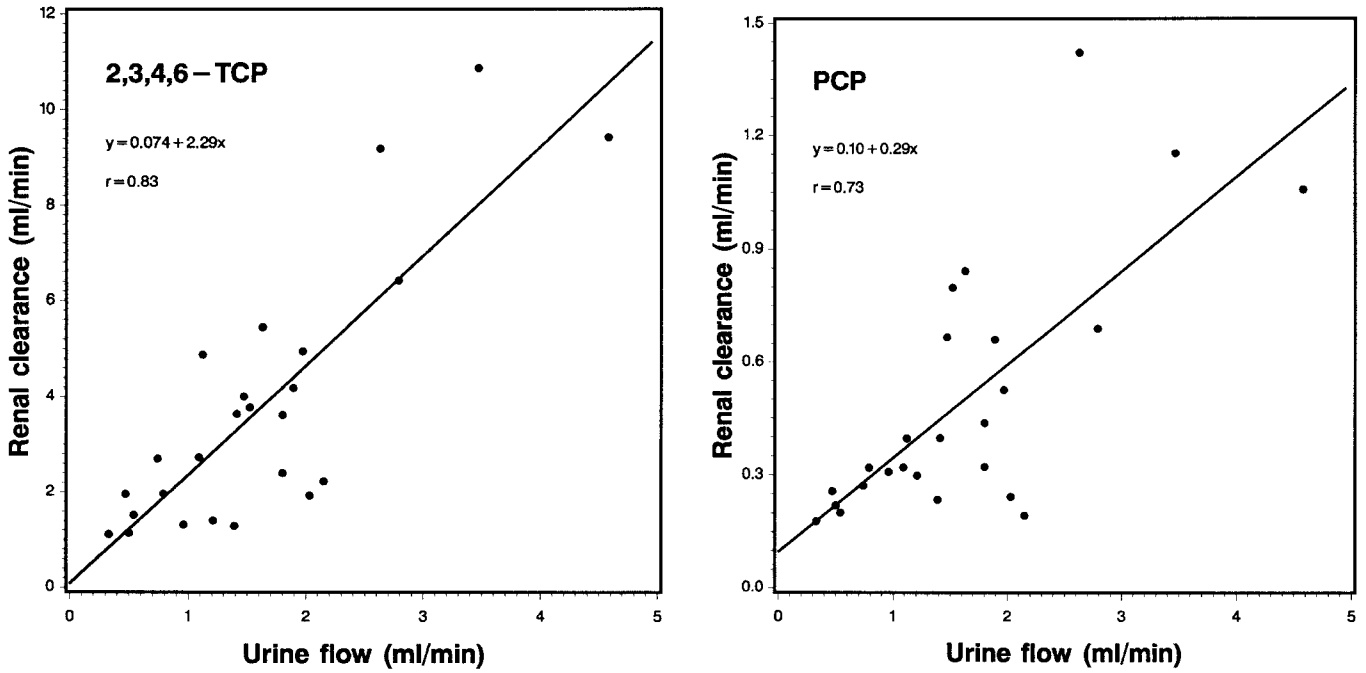

Fig. 3. Renal clearance of 2,3,4,6,-tetra- (*2,3,4,6-TCP, left*) and pentachlorophenol (*PCP, right*) as a function of urine flow. The serum chlorophenol concentration used was the average of the two daily measurements

Table 4. Type and extent of chlorophenol conjugation in the urine of exposed workers according to level of concentration

Group		Total acid hydrolysis[a]	Glucuronides + sulfates	Sulfates	Proportion of sulfates (%)
TriCP	I	0.6 ± 0.44	0.5 ± 0.41	0.5 ± 0.45	93.1 ± 34.16
	II	3.6 ± 1.31	3.5 ± 1.53	3.6 ± 1.67	104 ± 7.73
	III	12.6 ± 9.14	12.4 ± 9.64	13.6 ± 13.71	100.5 ± 14.21
TCP	I	0.6 ± 0.51	0.6 ± 0.51	0.6 ± 0.53	94.5 ± 11.45
	II	7.4 ± 3.85	8.3 ± 4.01	7.8 ± 3.45	97.7 ± 5.2
	III	26.7 ± 9.73	31.8 ± 12.56	31.3 ± 13.17	89.7 ± 15.88
PCP	I	0.1	< 0.1	0.01	50
	II	0.4 ± 0.28	0.2 ± 0.25	0.3 ± 0.23	93.9 ± 48.79
	III	2.3 ± 0.93	1.9 ± 0.74	1.6 ± 1.27	73.3 ± 52.23

[a] Total acid hydrolysis over 60 min at 100°C

Group I: 0.2–1.4, 0.2–1.5, and < 0.1 μmol/l; group II: 2–6, 2.8–12.6, and 0.2–1 μmol/l; group III, 6.4–34.4, 11.4–43, and 1.6–4.1 μmol/l for 2,4,6-trichlorophenol (TriCP), 2,3,4,6-tetrachlorophenol (TCP), and pentachlorophenol (PCP), respectively. Enzymatic hydrolysis was done with β-glucuronidase (glucuronides plus sulfates), and with β-glucuronidase in the presence of D-glucaro-1,4-lactone (sulfate conjugates)

concentrations of chlorophenols may be detected in the ground in the vicinity of sawmills [16, 23]. This exposure from the surroundings probably affects the half-time values calculated for tetrachloro- and pentachlorophenols to some extent: the observed half-times are probably higher than the true values.

The relatively high concentrations of pentachlorophenol detected in serum in relation to the small proportion in the technical chlorophenol product used in the sawmill shows that pentachlorophenol accumulated in serum, in line with calculated half-times. Empree and co-workers [9] also noted a difference in the composition of the chlorophenols between the technical product and the biological samples. According to their work, the accumulation of pentachlorophenol was strongest in serum.

The renal clearance was approximately 5 times faster for tetra- than for pentachlorophenol, and for both compounds the clearance increased linearly with the rate of urinary excretion. The minimal clearance values were 1.1 ml/min for tetrachloropherol and 0.2 ml/min for pentachlorophenol. Calculation of the clearance using total rather than unconjugated chlorophenol concentrations in serum is probably not entirely accurate due to different treatment by the kidney of the free and conjugated forms. However, since it is likely that the liver is the site of glucuronidation and that most chlorophenol in the blood is therefore in the conjugated form, these results indicate a marked saturable reabsorption of both chlorophenols in kidney tubules. The difference in clearance of tetra- and pentachlorophenols may also partly be due to their different binding affinities to plasma proteins; plasma protein binding of chlorophenols was enhanced by the increasing level of chlorination [11, 14, 25]. For trichlorophenol, no renal clearance could be calculated due to fluctuating serum levels.

In the normal population of Barcelona the conjugation of pentachlorophenol was found to be > 85% [10]. In our study, pentachlorophenol in urine was conjugated to a smaller extent than either tetra- or trichlorophenols. This may, however, be caused by the instability of the glucuronides of pentachlorophenol in urine [18]. It seems that after the long exposure period in the summer, the extent of conjugation of tri- and tetrachlorophenol was higher than that in the spring during the 1st week of exposure. One might speculate that the well-known adaptative increase in the activity of UDP-glucuronosyltransferase [8] might play a role in this finding.

Sulfate conjugation clearly dominates at low urinary concentrations, but when chlorophenol concentration increases, acid conjugation becomes more important. Sulfate conjugation has a high affinity but also a low capacity for phenol [6].

The half-time for pentachlorophenol in plasma of the rat is reported to be 20 h [1] and after single intraperitoneal administration (10 mg/kg), 2,3,5,6-tetrachlorophenol is eliminated with 24 h and 2,3,4,6,-tetrachlorophenol, within 48 h [5]. The approximate half-time calculated from these results for tetrachlorophenol isomers is 3–5 h. The half-time of 2,4,6-trichlorophenol in the tissues of the rat is between 1.4 and 1.8 h [21]. The urinary half-times for tri-, tetra-, and pentachlorophenol in humans, 18 h, 4.3 days and 16 days, respectively, follow the same pattern, matching well in the series of decreasing chlorine content and increasing water solubility.

The half-times of the chlorophenols differed considerably from each other. The shorter half-time of 2,4,6,-trichlorophenol, especially in comparison with tetra- and pentachlorophenol, has important implications for biological monitoring of chlorophenol exposure. Specimen collection for the analysis must take place rather soon after the cessation of the exposure; otherwise, the trichlorophenol that is rapidly excreted may go undetected.

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