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HYDROLYSIS AND BINDING OF A TOXIC STEREOISOMER OF SOMAN IN PLASMA AND TISSUE HOMOGENATES FROM RAT, GUINEA PIG AND MARMOSET, AND IN HUMAN PLASMA

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Abstract—The fallen concentration of one of the two isomers of soman (1,2,2-trimethylpropyl methylphosphonofluoridate), i.e., C(+)P(−)-soman, was investigated in plasma and in homogenates of brain, lung, liver, kidney, diaphragm, skeletal muscle and mucosa of small intestines from rat, guinea pig and marmoset, and in human plasma (pH 7.5, 37°). The decrease of the isomer concentration was followed by gas chromatographic determination of the residual concentration and proceeded in two phases due to a very rapid saturation of covalent binding sites for the isomer followed by catalysed hydrolysis. Estimates for the concentrations of covalent binding sites were obtained, which were relatively high in liver and kidney. Time periods for the hydrolysis of the isomer from a concentration of 40 ng/mL to 20 ng/mL were evaluated from the second reaction phase. It is concluded that the spontaneous and enzyme-catalyzed hydrolytic activities found for degradation of C(+)P(−)-soman in organs participating in central elimination are sufficiently high to account for the terminal half-life times of the isomer found in our toxicokinetic studies for the blood concentration after intoxication with 2–6 LD_{50} C(±)P(±)-soman. The hydrolytic activities are lower in the target organs for toxic action of soman, e.g., diaphragm and brain, especially for guinea pigs and marmosets.

From our toxicokinetic studies on C(±)P(±)-soman† (1,2,2-trimethylpropyl methylphosphonofluoridate) in rat, guinea pig and marmoset [1–3], it appeared that the toxic C(±)P(−)-isomers are rather persistent after administration of doses equivalent to 2–6 LD_{50} of the agent, with terminal half-life times in blood ranging between 10 and 60 min. The nontoxic C(±)P(+)-isomers are rapidly eliminated from blood. The main elimination pathways are covalent binding as well as phosphorylphosphatase-catalysed and noncatalysed hydrolysis. Covalent binding to highly reactive sites is the main process for the initial rapid elimination of the C(±)P(−)-isomers [2–4]. In the later elimination phase both covalent binding and hydrolysis may make a contribution.

In order to obtain more insight into the possible contribution of hydrolysis to the terminal elimination of the toxic isomers, hydrolysis in plasma and tissue homogenates has been investigated in the present work. For that purpose, the rate of hydrolysis was determined starting at an isomer concentration of *ca.* 40 ng/mL, i.e., corresponding with that present in blood after the initial rapid concentration decay following administration of 2–6 LD_{50} of C(±)P(±)-soman. The degradation of the single toxic C(+)P(−)-isomer has been investigated, since the rates of hydrolysis of both toxic C(±)P(−)-isomers were previously found to be similar in highly diluted plasma and liver homogenate from the three species [5].

In addition to the catalytic activities for C(+)P(−)-soman degradation in plasma of the three animal species, the activities were also studied in homogenates of liver, lung, kidney and mucosa of the small intestine, which are representative organs of the central compartment. Moreover, the rate of C(+)P(−)-soman degradation was determined in homogenates of brain, diaphragm and gastrocnemius et soleus muscles, which are representative target organs for the toxic activity of soman.

Hydrolysis was followed after saturation of the covalent binding sites in plasma and the tissue homogenates following reaction with C(+)P(−)-soman. An estimate of the total concentration of covalent binding sites for C(+)P(−)-soman in plasma and tissue is obtained from the rapid initial decline in the concentration of the isomer.

MATERIALS AND METHODS

Materials. C(+)P(−)-soman, C(±)P(+)-D_{13}-soman {C(±)P(+)-[U-^{2}H]1,2,2-trimethylpropyl methylphosphonofluoridate}, and 2,2-dimethylpropyl methylphosphonofluoridate were obtained as described previously [6, 7]. All other chemicals were

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† C stands for the asymmetric pinacolyl carbon and P for the asymmetric phosphorus atom; (+) and (−) are the two configurations around each atom and (±) stands for a mixture of the two configurations in any ratio.

obtained commercially including essentially fatty acid free bovine serum albumin (Sigma Chemical Co., St Louis, MO, U.S.A.).

Human blood was obtained from volunteers in our laboratory by venapuncture.* Blood of male albino rats (WAG/Rij), bred in the TNO Medical Biological Laboratory, and of male guinea pigs (Dunkin–Hartley type, Charles River, Sultzfeld, Germany) was obtained by heart puncture under anaesthesia with halothane (2.5%) in N_2O/oxygen (62:38) followed by hexobarbital (40 mg/kg, i.p.). Blood of marmosets (*Callitrix jacchius*), obtained from the Primate Center TNO, was taken via a carotid cannula after ketamine hydrochloride (100 mg/kg, i.m.) anaesthesia. Plasma was prepared by centrifugation for 20 min at 1200 *g*. After collection of blood from the animals, organs of interest were removed. Part of the small intestine was rinsed and the mucosa was scraped off. Homogenates were made 25% (w/w), or 10% for diaphragm and gastrocnemius et soleus muscles, in 0.01 M veronal buffer containing 0.9% (w/v) sodium chloride, pH 7.5, with a Polytron PT 10S homogenizer.†

Hydrolysis experiments. Reactions were started by addition of 1–20 μL of an appropriate C(+)P(−)-soman solution in ethyl acetate or acetonitrile to 1–4 mL plasma or homogenate equilibrated at pH 7.5 and 37°. Small volumes of 1 N NaOH or 0.1 N HCl were added if necessary to maintain the pH at 7.5 ± 0.1. Samples (70–200 μL) were taken from the reaction mixture after various times to follow the decrease of C(+)P(−)-soman concentration. For determination of the concentration at zero time of reaction, a sample of (2–100 μL) was taken from 0.01 M veronal-buffered saline to which the C(+)P(−)-soman solution in ethyl acetate or acetonitrile was added. For work-up, samples were mixed with 600 μL of the stabilizing acetate buffer containing aluminium sulphate, 2,2-dimethylpropyl methylphosphonofluoridate (0.6 μg), and the internal standard C(±)P(+)-D_{13}-soman (4 ng), before extraction over Sep-Pak C_{18} cartridges (Waters, Millipore Corporation, Milford, MA, U.S.A.) and desorption of the analytes with ethyl acetate (1 mL), as described previously for blood samples [6]. The eluates were analysed by gas chromatography (*vide infra*).

Hydrolysis reactions of C(+)P(−)-soman in buffer and in buffer containing bovine serum albumin were carried out in a similar manner.

Evaluation of kinetic parameters. For a few experiments, kinetic parameters were evaluated by plotting the two-exponential function

$$[\text{C(+)P(−)-soman}] = c_1 \cdot \exp(-c_2 t) + c_3 \cdot \exp(-c_4 t) \quad (1)$$

to the data obtained. Half-life times for the binding reaction and for the hydrolytic degradation of C(+)P(−)-soman were calculated from the exponential parameters c_2 and c_4. The concentration of binding sites was obtained as the pre-exponential parameter (c_1 or c_3) evaluated for the most rapidly decreasing term. Kinetic parameters from the other experiments were obtained by using a second-order polynomal function

$$\log [\text{C(+)P(−)-soman}] = a_0 + a_1 t + a_2 t^2 \quad (2)$$

to the data points. The time interval needed for the concentration decrease from 40 to 20 ng/mL [t(40–20)] was calculated according to

$$t(40\text{–}20) = [-\{a_1^2 - 4a_2 \cdot (a_0 - \log 20)\}^{1/2} + \{a_1^2 - 4a_2 \cdot (a_0 - \log 40)\}^{1/2}] \cdot \{1/(2a_2)\} \quad (3)$$

as can be derived from Equation 2. The concentration of binding sites for C(+)P(−)-soman in plasma or homogenate was evaluated as the difference between the initial concentration of C(+)P(−)-soman calculated from the amount added to the reaction mixture and the value obtained for a_0.

Protein determinations. Protein concentrations in plasma and organ homogenates were determined according to Bradford [8] using diluted (200–670-fold) homogenate or plasma (0.1 mL) and the Coomassie Brilliant Blue G reagent (1 mL), which was filtered before use. Calibration curves were made with bovine serum albumin (1–12.5 μg).

Gas chromatographic analysis. Gas chromatographic analyses were performed on a CPSil 8 CB fused silica capillary column (length, 51 m; i.d., 0.32 mm; film thickness, 1.3 μm) as described previously [5]. The column separates the enantiomeric pairs of C(±)P(±)-soman and the epimers of the internal standard C(±)P(+)-D_{13}-soman.

RESULTS

Hydrolytic activities

The decrease of the C(+)P(−)-soman concentration in tissue homogenates from rat, guinea pig and marmoset, in plasma of these species, and in human plasma proceeded in two phases. Usually, the first phase terminates within 2 min. This is probably due to a rapid reaction of a fraction of the isomer with a limited number of covalent binding sites, particularly carboxylesterases [9]. In a few cases, this first phase was slow enough to be followed with time (see Fig. 1 for an example). Half-life times for covalent binding and for hydrolytic degradation of C(+)P(−)-soman as well as the concentration of covalent binding sites were evaluated by fitting a two-exponential function (Equation 1) to the data obtained.

For most of the remaining experiments the slow hydrolytic phase could be described adequately by first-order kinetics (see Fig. 2 for an example). An obvious acceleration or retardation in the course of the reaction was observed in some homogenates and plasmata. These experiments were analysed by fitting a second-order polynomal function (Equation 2) to the data points of the second phase of the C(+)P(−)-soman concentration decrease. This is the equation for description of a first-order process extended by a term for correction of deviations from first-order kinetics ($a_2 t^2$). The time interval needed for the concentration decrease from 40 to 20 ng/mL has been taken as a measure for the catalytic activity of

* The experiments were approved by the TNO Committee dealing with ethical aspects for experiments on humans.

† The protocol for animal experiments was reviewed and approved by the TNO Animal Care Committee.

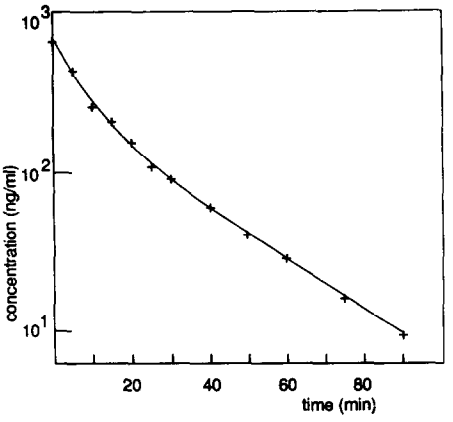

Fig. 1. Semilogarithmic plot of the decrease of C(+)P(−)-soman concentration in a 25% homogenate of rat lungs at pH 7.5 and 37°. The line represents the optimal fit of a two-exponential function to the data.

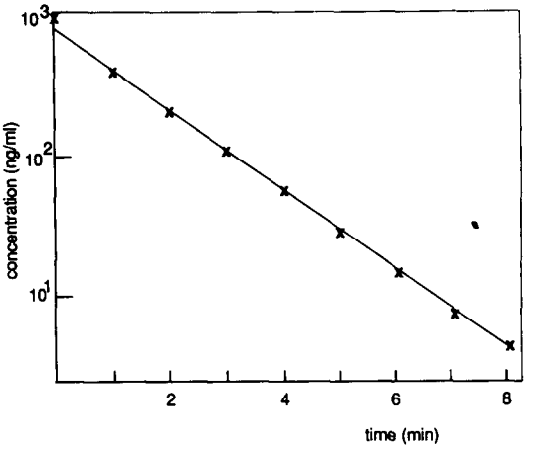

Fig. 2. Semilogarithmic plot of the decrease of C(+)P(−)-soman concentration in a 25% homogenate of marmoset kidneys at pH 7.5 and 37°. The line represents the optimal fit of a second-order polynomal function to all data except the data point for time zero.

plasma or homogenate. This time interval and the concentration of covalent binding sites were evaluated from the parameters obtained for the polynomal function.

A survey of the hydrolytic results is given in Table 1. Most often, the degradation of C(+)P(−)-soman (second phase) can be described according to first-order kinetics. An obvious acceleration was found in guinea pig plasma and in the homogenates of guinea pig liver (Fig. 3) and of rat mucosa.

In rat plasma, the catalytic activity decreases during incubation with C(+)P(−)-soman. Ultimately, the degradation proceeds according to first-order kinetics at a relatively slow rate (half-life time is 62 ± 5 min; see Fig. 4). This decrease varies with the nature of the organic solvent of the C(+)P(−)-soman stock solution added to initiate the reaction. The initial half-life time of hydrolysis, i.e., the half-life time for the noninhibited reaction, determined in the presence of a very low ethyl acetate concentration (0.007–

Table 1. Time period for hydrolysis of C(+)P(−)-soman concentration from 40 to 20 ng/mL [t(40–20)]* in 25% homogenates† of various organs from rat, guinea pig and marmoset, in plasma of these species, and in human plasma, at pH 7.5 and 37°

	Rat		Guinea pig		Marmoset		Human	
Organ	t(40–20) (min)	Dev	t(40–20) (min)	Dev	t(40–20) (min)	Dev	t(40–20) (min)	Dev
Plasma	4.5 ± 0.1§	+	7 ± 1	+	4.6 ± 0.8	−	35 ± 4 (4)	−
Lungs	17 ± 4 (4)	−‖	29 ± 7	−	21.7 ± 0.4 (4)	−		
Liver	46 ± 2 (4)	−	2.4 ± 0.5	+	1.4 ± 0.4 (4)	−		
Kidneys	76 ± 6 (4)	−	11 ± 1	±	1.1 ± 0.1	−		
Mucosa¶	13 ± 1	+	9 ± 4	−‖	4.3 ± 0.4	±		
Brain	34 ± 2	±	72 ± 14	−	30 ± 2 (4)	−‖		
Diaphragm†	81 ± 4	±	24 ± 2	−	57 ± 12	−		
Skeletal muscle†**	81 ± 2	−	81 ± 15 (4)	−	60 ± 4	−		

The extent to which the course of C(+)P(−)-soman decay deviates from first-order kinetics (dev‡) is indicated.

* Means ± SD, N = 3 unless otherwise noted in parentheses.

† Homogenates of diaphragm and skeletal muscles were 10%.

‡ −, $|a_2 t_i^2| < 0.2$; ±, $0.2 < |a_2 t_i^2| < 0.5$; +, $|a_2 t_i^2| > 0.5$. a_2 was found from curve fitting of Eqn (2) to data points and t_i is the time period during which the decrease of the C(+)P(−)-soman concentration was followed.

§ Calculated as (ln 2)/a_1, which is the half-life time for degradation at time zero. Terminal half-life of degradation was 62 ± 5 min (see also text).

‖ A two-exponential function was fitted to the data obtained for the decrease of C(+)P(−)-soman concentration, describing both binding and degradation of the isomer.

¶ Mucosa of small intestine.

** Gastrocnemius et soleus muscles.

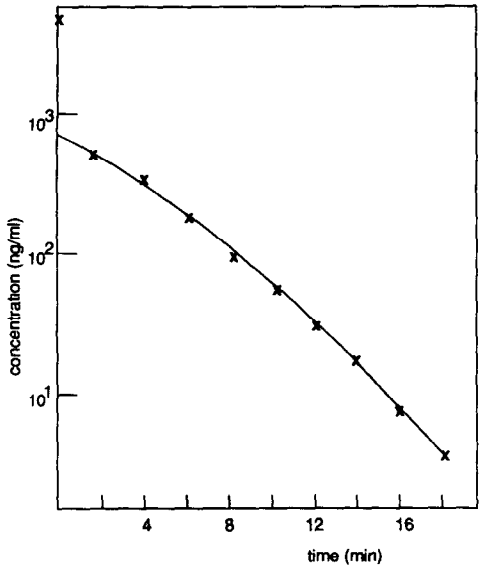

Fig. 3. Semilogarithmic plot of the decrease of C(+)P(−)-soman concentration in a 25% homogenate of guinea pig liver at pH 7.5 and 37°. The line represents the optimal fit of a second-order polynomal function to all data except the data point for time zero.

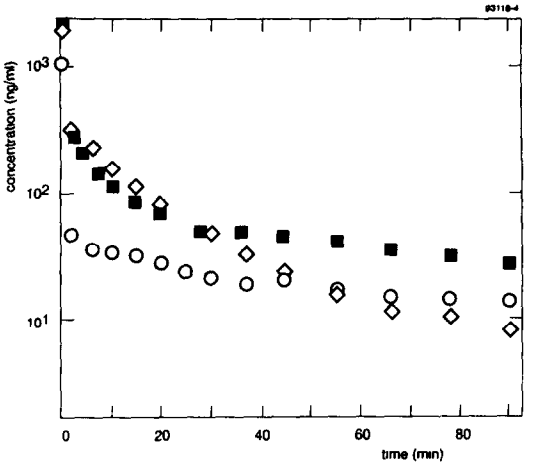

Fig. 4. Semilogarithmic plots of the decrease of C(+)P(−)-soman concentration in rat plasma at pH 7.5 and 37°. The reactions were initiated by addition of an aliquot of a C(+)P(−)-soman solution in ethyl acetate (◇, final concentration of ethyl acetate 0.1%), of an aliquot of a C(+)P(−)-soman solution in ethyl acetate diluted 100-fold in veronal-buffered saline (■, final concentration of ethyl acetate 0.008%), and of an aliquot of a C(+)P(−)-soman solution in acetonitrile (○, final concentration of acetonitrile 0.2%).

0.008%) was used to characterize the catalysed degradation of the isomer in rat plasma. At a higher final ethyl acetate concentration (0.10–0.17%), the decrease proceeds at a slower rate, but the initial half-life time is less (Fig. 4). An even more distinct inactivation was found after addition of a C(+)P(−)-soman stock solution in acetonitrile (final concentration 0.2%; see Fig. 4).

Concentrations of binding sites

In a number of cases, the present experiments also allowed for an estimation of the concentration of binding sites for C(+)P(−)-soman in plasma and the homogenates. The data obtained are presented in Table 2. The set-up of our experiments aimed primarily at the determination of the rate of degradation of the isomer and was therefore not suitable for an accurate estimation of small concentrations of binding sites. This is illustrated by the large error in the amount of binding sites when binding is low. In some runs, the decrease of the C(+)P(−)-soman concentration was insufficient to evaluate t(40–20). However, the concentration of binding sites could be estimated in these runs from the rapid initial concentration decrease. Therefore, the quantity of binding sites in some organs was calculated as an averaged value from a larger number of experiments than the value for t(40–20) (compare Tables 1 and 2). For rat plasma, the concentration of binding sites was evaluated as the average of the values obtained from experiments carried out in the presence of low (0.007–0.008%) as well as of higher (0.10–0.17%) final concentrations of ethyl acetate.

Nonspecifically catalysed degradation of C(+)P(−)-soman in plasma and organ homogenates

It is known that hydrolysis of organophosphates is catalysed nonspecifically by some buffer constituents, particularly phosphate and bicarbonate ions, and by albumin [10, 3]. In order to estimate the relative contributions of nonenzymatic catalysis, a series of experiments was carried out on the hydrolysis of C(+)P(−)-soman in Krebs-Ringer buffer and in veronal-buffered saline, both containing various concentrations of bovine serum albumin. It is assumed that the effect of albumin on the rate of hydrolysis of C(+)P(−)-soman is similar to the nonenzymatic hydrolysis by the protein in plasma or homogenate. Krebs-Ringer buffer is used as a medium to determine blank values for nonenzymatically catalysed hydrolysis in plasma. Veronal-buffered saline is the medium in which the organs were homogenized. The rate constants are given in Table 3.

The two rate constants obtained for hydrolysis in Krebs-Ringer buffer were used to interpolate blank values for nonspecifically catalysed hydrolysis in plasma. Interpolated blank values in veronal-buffered saline were calculated from the second-order polynomal equation* fitted to the rate constants determined for hydrolysis of C(+)P(−)-soman in this medium at various albumin concentrations.

* Rate constant (10^{-3} min) = 1.85 + 0.267 [albumin] − 0.0015 [albumin]^2 (albumin concentration in mg/mL).

Table 2. Concentration of covalent binding sites for C(+)P(−)-soman in plasma and organs of rat, guinea pig and marmoset, and in human plasma, obtained from determinations (pH 7.5, 37°) in plasma and organ homogenates (25%)*

Organ	Concentration of binding sites [ng C(+)P(−)-soman equivalents/g organ or plasma ± SD]†			
	Rat	Guinea pig	Marmoset	Human
Plasma	920 ± 150 (6)	160 ± 20 (4)	1 ± 1	17 ± 5 (4)
Liver	9000 ± 2000 (4)	12,000 ± 2000 (4)	2500 ± 400 (4)	
Lungs	1250 ± 480 (4)‡	50 ± 90	40 ± 30 (4)	
Kidneys	2200 ± 200 (7)	2000 ± 600 (4)	600 ± 120	
Mucosa§	560 ± 60	2000 ± 100‡	90 ± 30	
Brain	20 ± 30	20 ± 30 (4)	130 ± 30 (4)‡	
Diaphragm	110 ± 70 (4)	330 ± 40	20 ± 40	
Skeletal muscle‖	86 ± 3	60 ± 60 (4)	20 ± 20	

* Homogenates of diaphragm and skeletal muscle were 10%.

† N = 3 unless otherwise noted in parentheses.

‡ A two-exponential function was fitted to the data for decrease of C(+)P(−)-soman concentration, describing both binding and degradation of the isomer. Rate constants for binding additionally obtained from this evaluation are: 0.18 ± 0.07, 0.47 ± 0.03, and 0.12 ± 0.04 min^{-1} for the homogenates of rat lungs, guinea pig mucosa and marmoset brain, respectively.

§ Mucosa of small intestine.

‖ Gastrocnemius et soleus muscles.

Table 3. Rate constants* for hydrolysis of C(+)P(−)-soman in Krebs-Ringer buffer and in veronal-(0.01 M) buffered saline containing various concentrations of bovine serum albumin, at pH 7.5 and 37°

Buffer	Albumin concentration (mg/mL)	Rate constant (10^{-3} min^{-1})
Krebs-Ringer	40	15 ± 2
	75	24 ± 1
Veronal/saline	—	2.0 ± 0.1
	10	4.1 ± 0.8
	25	7.8 ± 0.5
	55	12.0 ± 1.2 (4)

* Means ± SD, N = 3 unless otherwise noted in parentheses.

DISCUSSION

In general, rather high overall rates of C(+)P(−)-soman degradation have been found in plasma and in homogenates or organs that are part of the central compartment, i.e., liver, kidney and mucosa. However, the degradation proceeds relatively slowly in rat liver and rat kidney. The much slower degradation in kidney homogenate of the rat than in those of the two other species is consistent with the much higher C(±)P(−)-soman concentrations found in rat kidneys and urine 1–4 hr after intravenous administration of C(±)P(±)-soman [3]. The levels were at least two orders of magnitude higher than the corresponding levels in the two other species after administration of both equitoxic (6 LD_{50}) and similar absolute doses. Also in human plasma, the overall degradation is rather slow, particularly when compared to the degradation rates in plasma of the other species. The overall hydrolytic activities in the homogenates of organs that are considered to be target organs for the toxic action of soman, i.e., brain, diaphragm and skeletal muscle, are much lower than those in homogenates from organs of the central compartment, even when it is taken into account that the muscle homogenates are 2.5-fold more dilute than the other homogenates.

The value obtained for the overall rate of degradation of C(+)P(−)-soman in human plasma is in reasonable agreement with the rate reported by De Bisschop *et al.* [11] for hydrolysis at pH 7.4–7.6 and 37° at an initial concentration of C(+)P(−)-soman of 5 ng/mL in 50% human plasma/Tris buffer (1:1, v/v), i.e., a half-life time of 43 min. The relative hydrolytic activities in plasma of the four species and those in liver homogenates of the three species do not correspond to those obtained from previous experiments [5] carried out with highly diluted plasma and homogenates and with relatively high C(+)P(−)-soman concentrations. Previously, the relative order was rat plasma > marmoset plasma > human plasma > guinea pig plasma, and rat liver homogenate > guinea pig and marmoset liver homogenates. This discrepancy might be due to the large differences between the previous and the present experiments with regard to both the concentrations of hydrolytic enzymes (dilutions of plasma and liver homogenates) and the concentrations of C(+)P(−)-soman.

The ratios of nonspecifically catalysed hydrolysis (Table 3) and that of the overall rate of degradation (Table 1) may be taken as a semiquantitative measure of the extent of acceleration of C(+)P(−)-soman degradation by enzyme catalysis in plasma or homogenate. These values, given in Table 4, indicate that hydrolysis of C(+)P(−)-soman due to enzyme

Table 4. Acceleration by enzyme catalysis of the degradation of C(+)P(−)-soman in plasma and 25% organ homogenates of various species*

Organ	t(nonenzymatic catalysis)/t(40–20)			
	Rat	Guinea pig	Marmoset	Human
Plasma	9	7	8	0.8
Liver	1	24	40	
Lungs	5	3	4	
Kidneys	1	7	83	
Mucosa‡	14	12	22	
Brain	4	2	5	
Diaphragm*	3	9	4	
Skeletal muscle*§	2	2	2	

The acceleration is expressed as the ratio between the half-life time for nonenzymatically catalysed hydrolysis [t(nonenzymatic catalysis)]† and the time for decrease of C(+)P(−)-soman concentration from 40 to 20 ng/mL [t(40–20)].

* Homogenates of diaphragm and skeletal muscle were 10%.

† This half-life time was obtained from hydrolysis in Krebs-Ringer buffer or veronal-buffered saline at an albumin concentration corresponding to the total protein concentration in plasma or homogenate, respectively.

‡ Mucosa of small intestine.

§ Gastrocnemius et soleus muscles

catalysis proceeds only somewhat faster than hydrolysis by nonenzymatic catalysis in plasma and most homogenates. Considerable enzyme activities have been found only in the homogenates of marmoset kidney, of guinea pig and marmoset liver, and of the intestinal mucosa of all three species.

The largest quantities of binding sites were found in the liver (Table 2). Substantial amounts are also present in the kidneys of the three species, in mucosa from rat and guinea pig, and in rat plasma and lungs. The amount of binding sites in plasma and most organs of marmoset is less than in plasma and the corresponding organs of the two other species.

The concentrations of binding sites in rat and guinea pig plasma as obtained in the present experiments from reaction with C(+)P(−)-soman are in reasonable agreement with those reported by Christen and Cohen [12] from *in vitro* experiments with [^{32}P]sarin (isopropyl [^{32}P]methylphosphonofluoridate). They found concentrations of 3.5 and 1.1 μM in rats and guinea pigs, corresponding to binding capacities of 640 and 200 ng C(+)P(−)-soman/mL, respectively. Our value for human plasma is much lower than the binding capacity reported by these authors, i.e., 0.7 μM corresponding to a binding capacity for 130 ng C(+)P(−)-soman/mL. However, our value is in agreement with the concentration obtained by De Bisschop *et al.* [13] from *in vitro* binding studies using C(±)P(±)-soman, i.e., a binding capacity of 13 ng C(±)P(±)-soman/mL.

Maxwell and co-workers [9, 14] estimated the concentrations of carboxylesterase-active sites from the enzyme activities measured in various rat tissues, assuming similar catalytic activities per active site for enzymes from different tissues. These estimates are in agreement with the concentrations of binding sites that we found for C(+)P(−)-soman (Table 2). Only the present value for the quantity of binding sites in lungs is almost 2-fold smaller than the value estimated by Maxwell *et al.* [9].

The low overall activities found in plasma and homogenates of organs of the three species for hydrolytic degradation of the C(±)P(−)-isomers suggests that the contribution of this pathway to the elimination of the toxic soman isomers can be neglected in the acutely toxic phase, i.e., immediately after administration of the agent. A negligible role of catalysed hydrolysis is also suggested by the inverse relationship observed between the relative catalytic activities of C(+)P(−)-soman degradation in plasma and homogenates of organs participating in the central elimination from the three species (marmoset > guinea pig > rat) and the acutely lethal doses of soman in these species (marmoset < guinea pig < rat).

On the basis of the present results, however, degradation might contribute to elimination in a later phase, e.g., during treatment of the intoxication. If so, this contribution is probably smaller in the target organs for toxic action of soman (brain, diaphragm, skeletal muscles) than in organs participating in the central elimination, as indicated by the often lower overall activities in the target organs than in the central organs, especially for guinea pig and marmoset. This may cause a higher persistence of the toxic isomers in the target organs. This persistence is probably strengthened by the low concentrations of binding sites in these organs relative to those in the organs participating in central elimination.

The present results do not allow us to conclude whether binding or degradation is the major pathway or elimination in the later phase of the toxicokinetics of the toxic soman isomers. However, the overall activities for degradation of C(+)P(−)-soman in a number of organs participating in central elimination are sufficiently high to account for the terminal half-life times of at least 10 min found for the blood concentration of the isomer after intoxication of the species with 2–6 LD_{50} C(±)P(±)-soman [2].

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