Distribution of Methyl Sulfone Metabolites of Polychlorinated Biphenyls and p,p’-DDE in Human Tissues

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We determined methylsulfonyl metabolites of chlorinated biphenyls (MeSO2-CBs) and 1,1-bis(4-chlorophenyl)-2,2-dichloroethene (p,p’-DDE) in human adipose, liver, brain, and lung tissues obtained from 11 Belgian individuals (9–62 years of age). The total concentration of MeSO2-CBs (lipid weight basis) decreased in the following order: liver (mean, 9.30 ng/g; range, 1.68–27.03 ng/g lipid) > lung (mean, 2.72 ng/g; range, not detected (ND) to 11.54 ng/g lipid) > adipose tissue (mean, 1.57 ng/g; range, 0.33–4.33 ng/g lipid) > brain (mean, 0.24 ng/g; range, ND–0.56 ng/g lipid). The profiles of MeSO2-CBs and MeSO2-DDE in each tissue were similar for all 11 subjects. In adipose, brain, and lung tissues, 4’-MeSO2-CB87, 4’-MeSO2-CB101, and 3-MeSO2-CB149 were by far the most abundant conglomerate in liver, contributing on average to approximately 60% of the sum of MeSO2-CBs. The concentrations of 3-MeSO2-DDE in different tissues were at the same or lower levels than the total concentrations of MeSO2-CBs. This study suggests that the distribution patterns of MeSO2-CBs and MeSO2-DDE in humans differ between liver and other tissues. Moreover, these profiles differ from those found in other mammals, such as polar bears, porpoises, and otters. Key words: adipose tissue, brain, DDE, humans, liver, lung, methyl sulfone, PCBs. Environ Health Perspect 111:1222–1227 (2003). doi:10.1289/ehp.6141 available via http://dx.doi.org/ [Online 6 March 2003]

Polychlorinated biphenyls (PCBs) and 1,1-bis(4-chlorophenyl)-2,2-dichloroethene (p,p’-DDE) are well-known pollutants that have been found in many environmental matrices and in humans (Kimbrough and Jensen 1989; Turusov et al. 2002). Despite their persistence in the environment, PCBs and p,p’-DDE are susceptible to enzyme-mediated biotransformation in biota. Generally, an initial step in the PCB metabolism is the generation of an arene oxide intermediate. Further, two main metabolic pathways in mammals have been reported: the mercapturic acid pathway to give methyl sulfone (MeSO2) metabolites and hydroxylation to yield biphenylols (Letcher et al. 2000a). Although the major metabolic route is hydroxylation generally followed by excretion, significant amounts of methylsulfonyl metabolites of chlorinated biphenyls (MeSO2-CBs) and of DDE (MeSO2-DDE) may be accumulated in tissues because of their lipophilic character and specific protein-binding properties (Jönsson et al. 1994; Lund et al. 1985, 1988). MeSO2-CBs and MeSO2-p,p’-DDE have been mostly quantified in fat and liver tissues (Letcher et al. 2000a, 2000b), whereas hydroxylated PCBs were mostly determined in blood (Letcher et al. 2000a).

MeSO2-CBs and MeSO2-DDE were detected in several wildlife species (Bergman et al. 1994; Haraguchi et al. 1988; Jensen and Jansson 1976; Stapleton et al. 2001) and in human breast milk (Nørén and Meironyté 1976; Yeshida and Nakamura 1977), blood (Nørén et al. 1996, 1999; Weistrand et al. 1997), and other tissues (Ellerichmann et al. 1998; Haraguchi et al. 1986; Weistrand and Nørén 1997, 1998).

The biologic activities and toxicologic significance of methylsulfonyl metabolites have been recently reviewed (Letcher et al. 2000a). It has been shown that 3’-MeSO2-CB87 and 3’-MeSO2-CB101, but not their corresponding 4’-MeSO2-metabolites, induced hepatic CYP2-family protein levels and related catalytic activities in rats (Letcher et al. 2000a). Moreover, the potential of persistent MeSO2-CBs to influence endocrine-related processes has been demonstrated (Letcher et al. 2000a). 3’-MeSO2-CB132, 3’-MeSO2-CB141, 3-MeSO2-CB149, and 4’-MeSO2-CB149 reduced thyroid hormone levels in blood and increased thyroid weight and hepatic CYP protein levels in rats (Kato et al. 2000).

It was previously shown that the distribution of methylsulfonyl metabolites depends on both the congeners structure and the species-specific metabolic capacity (Letcher et al. 1998; Stapleton et al. 2001). In experimental animals, it was demonstrated that MeSO2-CBs might also have specific protein-binding properties reflected by specific retention in the body, such as adrenal, lung, kidney tissues, and uterine fluid (Bergman et al. 1979; Brandt and Bergman 1987; Jönsson et al. 1994; Lund et al. 1985, 1988). Although specific accumulation in selected organs has been demonstrated in experimental animals dosed for a short period (no more than few weeks) (Brandt et al. 1982; Jönsson et al. 1992), it is difficult to relate it to the distribution of methylsulfonyl metabolites in humans. Although several MeSO2-CBs have been recently observed to be selectively and strongly retained in human liver (Norén et al. 1999; Weistrand and Norén 1997), the knowledge of accumulation and distribution of methylsulfonyl metabolites in other human tissues is still scarce.

The occurrence of MeSO2-CBs and MeSO2-DDE in wildlife and human samples and the demonstrated accumulation of certain MeSO2-CBs and MeSO2-DDE in specific tissues of mammals have made the investigation of these compounds in the environment important. In the present study, we have determined MeSO2-CB and MeSO2-DDE levels, together with PCBs and p,p’-DDE in different human tissues from Belgian individuals, to investigate their congenor distribution and correlation between metabolites and parent compounds.

Materials and Methods

Samples. Human tissues, including adipose, liver, lung, and brain, were collected in the first half of 2002 from 11 subjects during medicolegal autopsy. The subjects (8 men and 3 women) died suddenly from causes unrelated to environmental contamination, and the age of subjects ranged from 9 to 62 years (mean, 34 years; median, 30 years). The body weight ranged from 30 to 100 kg (mean, 71 kg; median, 75 kg). No information was available on the subjects’ diets or professions. Detailed information of the subjects is presented in Table 1. All of the samples were stored at −20°C until analysis.

Reagents and standards. All 26 individual standards of MeSO2-CBs and 3-MeSO2-DDE, together with 3-MeSO2-4-methyl-2,2’,3’,4’,5’-pentachlorobiphenyl (3-MeSO2-4-Me-CB), which was used as internal standard, were prepared at the Daiichi College of Pharmaceutical Sciences (Fukushima, Japan) as described by Haraguchi et al. (1987). The chemical names of MeSO2-CB congeners were simplified on the basis of the International Union of Pure and Applied Chemistry (IUPAC)-derived numbering system of the parent PCBs (Letcher et al. 2000a). All 29 individual PCB congeners and 3...
organochlorine pesticides \( p,p'-\)DDE, \( p,p'-\)DDD (dichlorodiphenyldichloroethane), and \( p,p'-\)DDT (dichlorodiphenyltrichloroethane) were purchased from Dr. Ehrenstorfer (Augsburg, Germany). All solvents (hexane, acetone, methanol, isoctane, and dichloromethane (DCM)) were of pesticide grade (Merck, Darmstadt, Germany). Concentrated sulfuric acid (H\(_2\)SO\(_4\); 95–97%), potassium hydroxide (KOH), and silica gel 60 (70–230 mesh) were obtained from Merck. Before use, anhydrous sodium sulfate (Na\(_2\)SO\(_4\); Merck) was heated at 600°C for 6 hr in a muffle furnace. Florisil (60–100 mesh) (Supelco, Bornem, Belgium) was activated at 130°C overnight and then deactivated with 2% (wt/wt) water. Silica gel impregnated with KOH (33% KOH, wt/wt) was prepared by dissolving KOH in methanol and adding it to dry silica gel. The solvent was then evaporated at 60°C, and the resulting silica gel was heated at 150–170°C before use. The acid silica (45%, wt/wt) was prepared by dropwise addition of concentrated H\(_2\)SO\(_4\) to dry silica gel under continuous stirring.

**Extraction and cleanup.** The sample preparation and analysis of MeSO\(_2\) metabolites were as reported elsewhere (Chu et al. 2002) and are briefly described here. The tissue samples (0.5 g adipose tissue or 5 g of other tissues) were thawed, quantitatively weighed, and dehydrated by grinding with anhydrous Na\(_2\)SO\(_4\) until a free-flowing powder was obtained. The samples were spiked with 100 µL × 10 pg/µL 3-MeSO\(_2\)-4-Me-CB as internal standard for MeSO\(_2\)-CBs and MeSO\(_2\)-DDE, and 100 µL × 100 pg/µL 2,2',3,6'-tetra-CB (CB46) and 2,2',3,4,5,6'-hexa-CB (CB143) as internal standards for PCBs and organochlorine pesticides. A Soxhlet system (B-811; BUCHI, Brussels, Belgium) was used in hot extraction mode for 4 hr with 100 mL hexane/acetone (3/1, vol/vol). After the extract was concentrated to approximately 10 mL and transferred to a centrifuge tube, an accurate portion (~10%) was removed for the gravimetric determination of lipid concentration. The remaining extract was concentrated, and the solvent was exchanged to hexane and reduced to a volume of 2 mL.

MeSO\(_2\)-CBs and MeSO\(_2\)-DDE were separated from other organochlorine compounds by liquid–liquid partitioning with concentrated H\(_2\)SO\(_4\). The hexane solution was extracted twice with 2 mL concentrated H\(_2\)SO\(_4\), and the acid phase was separated by centrifugation (4,000 rpm). The acid phases were combined and used for the determination of MeSO\(_2\)-CBs and MeSO\(_2\)-DDE, and the remaining hexane layer was used for the determination of PCBs and organochlorine pesticides.

For the determination of MeSO\(_2\)-CBs and MeSO\(_2\)-DDE, the combined sulfuric acid phase (~4 mL) was diluted with 4 mL cold distilled water. The solution was cooled, and the analytes were twice back-extracted with 2 mL hexane. The resulting organic layer was separated and washed with 2 mL NaCl solution (10%, wt/wt). The organic phase containing MeSO\(_2\)-CBs and MeSO\(_2\)-DDE was concentrated and loaded on a column packed with 1 g basic silica (33% KOH) and 5 g anhydrous Na\(_2\)SO\(_4\) and eluted with 10 mL DCM. The solvent was exchanged to hexane, concentrated to approximately 1 mL, and applied to a column (30 cm × 1 cm) filled with 8 g Florisil. The column was first eluted with 40 mL DCM/hexane (1:1, vol/vol), and 10 mL DCM, which were discarded. The MeSO\(_2\) metabolites were eluted with 40 mL DCM, and this fraction was collected and concentrated to approximately 2 mL. The purified extract was evaporated to dryness by a gentle stream of nitrogen at ambient room temperature. The residue was dissolved in 100 µL isoctane and then transferred to an injection vial.

**Table 1.** Details of the investigated human subjects \((n = 11)\).

| Subject no. | Sex | Age (years) | Weight (kg) |
|-------------|-----|-------------|-------------|
| 1           | Male | 9           | 30          |
| 2           | Male | 12          | 30          |
| 3           | Male | 22          | 70          |
| 4           | Male | 25          | 65          |
| 5           | Male | 25          | 100         |
| 6           | Male | 30          | 100         |
| 7           | Male | 32          | 75          |
| 8           | Female | 51         | 75          |
| 9           | Female | 51         | 75          |
| 10          | Male | 57          | 90          |
| 11          | Female | 62         | 75          |
| Mean ± SD   | 34 ± 18 | 71 ± 23     |             |

**Table 2.** Levels of MeSO\(_2\)-CBs and MeSO\(_2\)-DDE (ng/g lipid weight) in Belgian human tissues.

| Compound   | Chlorine substitution | LOD  | Adipose | Liver | Brain | Lung |
|------------|-----------------------|------|---------|-------|-------|------|
|            |                       |      | Range   | Mean  | Range | Mean |
| Lipid (%)  |                       |      | 65.0–87.7 | 79.5 | 2.8–14.0 | 7.3 |
| 3-MeSO\(_2\)-CB1 | 2,5-4'                | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB1 | 2,5-4'                | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB94 | 2,4-2'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB94 | 2,4-2'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB92 | 2,5-2'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB92 | 2,5-2'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB84 | 2,5-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB84 | 2,5-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB70 | 2,5-3'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB70 | 2,5-3'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB87 | 2,3-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB87 | 2,3-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB1 | 2,5-6'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB1 | 2,5-6'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB1 | 2,5-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB1 | 2,5-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB110 | 2,5-6'                | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB110 | 2,5-6'                | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB132 | 2,3-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB132 | 2,3-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB141 | 2,3-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB141 | 2,3-4'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB149 | 2,5-6'                 | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB149 | 2,5-6'                 | 0.06 | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-CB174 | 2,3,4-5'                | 0.06 | ND      | ND    | ND    | ND   |
| 4-MeSO\(_2\)-CB174 | 2,3,4-5'                | 0.06 | ND      | ND    | ND    | ND   |
| Sum MeSO\(_2\)-CBs | 0.10                   |      | ND      | ND    | ND    | ND   |
| 3-MeSO\(_2\)-DDE | 0.10                   |      | ND      | ND    | ND    | ND   |

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PCBs and organochlorine pesticides were determined as previously described (Covaci et al. 2002). The remaining hexane phase from the partitioning with concentrated H₂SO₄ was further cleaned on a column filled with 10 g acetic silica gel (45%, wt/wt), and the analytes were eluted with 30 mL hexane. After evaporation to dryness, the residue was dissolved in 100 µL isooctane and transferred to vials for gas chromatography/electron-capture detection (GC-ECD) and gas chromatography/mass spectroscopy (GC/MS) analysis.

**Determination of MeSO₂-CBs and MeSO₂-DDE by GC/electron-capture negative ionization MS.** An Agilent 6890 gas chromatograph (Agilent, Palo Alto, CA, USA) equipped with a 5973 quadrupole MS detector was used for the determination of MeSO₂-CBs and MeSO₂-DDE. The GC column was an AT-5MS capillary column 50 m × 0.18 mm internal diameter with a film thickness of 0.25 µm (Alltech, Lokeren, Belgium). Helium was used as carrier gas at a constant flow of 0.5 mL/min. Extract (2 µL) was injected in solvent vent mode. The injector temperature was held at 90°C for 0.3 min, heated at 600°C/min to 300°C, and then held for 20 min. The vent flow was 100 mL/min, and vent and purge times were 0.2 and 2 min, respectively. The oven temperature was programmed as follows: 80°C, held for 2.5 min, then at 20°C/min to 250°C, then at 5°C/min to 290°C, and finally held for 40 min. The transfer line and quadrupole temperatures were 250°C and 150°C, respectively. Ionization was performed in electron-capture negative ionization (ECNI) mode, using methane as reagent gas.

The fraction containing MeSO₂-CBs and MeSO₂-DDE was analyzed in the selected ion-monitoring mode, and the identification of analytes was based on their retention times and the ratios of monitored ions (Chu et al. 2002). Three most intense ions from M- and/or [M-Me]⁻ clusters were monitored (Chu et al. 2002). Twenty-six MeSO₂-CB congeners and MeSO₂-DDE, representing the majority of MeSO₂ metabolites identified so far in biota (Letcher et al. 2000a), were chosen for the method validation. Quantitative determination was done using a five-level calibration curve spanning the range of the analyte concentrations in real samples.

**Determination of PCBs and organochlorine pesticides by GC-ECD and GC/MS.** An Agilent 6890 GC with µ-cell ECD was used for the determination of PCBs and pesticides. The separation was performed on an HT-8 capillary column (25 m × 0.22 mm, 0.25 µm film thickness) from SGE (Darmstadt, Germany). The carrier and make-up gas were helium (1 mL/min) and argon/methane 95%/5% (40 mL/min), respectively. The oven temperature was programmed as follows: 90°C, held for 1 min, then to 180°C at 15°C/min, held for 1 min, to 250°C at 3°C/min, and then to 290°C at 15°C/min, held for 6 min. The injector and detector temperatures were 270°C and 320°C, respectively. One microliter of the extract was injected in pulsed splitless mode, and the purge time was 1 min. The identification was based on the retention time of individual standard congeners, and a multicalibration curve was used for quantitative determination.

For confirmation, all samples were analyzed by GC/MS with electron ionization source and selected ion-monitoring mode. An HP-1MS capillary column (30 m × 0.25 mm, 0.25 µm film thickness) was used for the separation of analytes. The oven temperature was programmed as follows: 90°C, held for 2 min, then to 200°C at 3°C/min, then to 290°C at 3°C/min, held for 20 min. The injector temperature was 300°C. One microliter of extract was injected in splitless mode, and the purge time was 1 min. Although GC/MS (electron ionization) analysis can give additional information concerning the analyte identification, its sensitivity was lower than that of GC-ECD. Therefore, the quantitative results were based on the ECD determination, except for a few pairs of PCB congeners and pesticides (e.g.,

| Compound | LOD | Adipose | Liver | Brain | Lung |
|----------|-----|---------|-------|-------|------|
| CB18     | 17.1| ND      | ND    | ND    | ND   |
| CB28     | 24.6| ND      | ND    | ND    | ND   |
| CB31     | 21.8| ND      | ND    | ND    | ND   |
| CB44     | 2.5 | ND–3.8  | ND    | ND–4.2| ND    |
| CB52     | 2.5 | ND–4.7  | 3.0   | ND–12.4| 4.5   |
| CB74     | 2.2 | 2.8–17.2| 8.2   | ND–33.1| 8.3   |
| CB87     | 1.0 | ND      | ND    | ND–9.5 | ND    |
| CB95     | 5.7 | ND      | ND    | ND–11.5| ND    |
| CB99     | 4.2 | 5.7–25.9| 12.1  | ND–25.4| 8.7   |
| CB101    | 1.0 | 1.2–7.0 | 3.6   | 1.8–6.7| 4.3   |
| CB105    | 3.6 | ND–16.1| 5.6   | 3.6–13.4| 6.8   |
| CB110    | 2.2 | ND–6.4 | 3.6   | ND–14.1| 7.6   |
| CB118    | 2.5 | 7.5–61.3| 20.3  | 5.5–56.2| 17.4  |
| CB129    | 0.7 | 0.9–7.0 | 2.3   | ND–4.4 | 2.4   |
| CB132    | 1.7 | ND–33.1| 10.6  | ND–26.0| 8.5   |
| CB138    | 3.0 | 21.0–135.9| 56.4 | 5.4–114.3| 34.6  |
| CB149    | 3.0 | ND–5.2 | 3.0   | ND–10.4| 4.9   |
| CB153    | 3.0 | 40.3–251.0| 108.6| 10.6–240.3| 77.6  |
| CB156    | 6.0 | ND–33.1| 13.7  | ND–27.6| 8.5   |
| CB163    | 4.8 | 14.5–70.1| 39.8 | ND–58.3| 25.4  |
| CB167    | 4.3 | ND–9.7  | ND    | ND–9.5 | ND    |
| CB170    | 1.2 | 10.0–59.1| 29.9 | 2.4–52.8| 21.1  |
| CB177    | 0.5 | 2.6–18.4| 7.1   | 0.8–17.5| 6.7   |
| CB180    | 2.6 | 29.3–161.8| 81.9 | 5.4–1429| 54.7  |
| CB183    | 0.8 | 4.5–24.1| 10.1  | 1.3–20.1| 6.7   |
| CB187    | 0.8 | 7.5–56.9| 23.6  | 2.4–54.6| 18.2  |
| CB194    | 0.4 | 5.0–36.5| 16.1  | 2.2–32.3| 12.0  |
| CB196    | 0.6 | 3.1–22.5| 10.1  | 1.0–16.7| 7.1   |
| CB199    | 0.2 | 2.3–20.4| 8.9   | 0.8–15.2| 5.8   |
| Sum PCBs | 185.7–1058.2| 479.6 | 79.9–931.6| 358.9 |
| p,p'-DDE | 20.0| 84.1–1782.1| 484.3| 100.4–1196.7| 468.9 |
| p,p'-DDT | 20.0| ND      | ND    | ND–120.0| 27.6  |
| p,p'-DDE | 20.0| ND–50.6| ND    | ND–22.0| ND    |

Table 3. Levels of PCBs and organochlorine pesticides (ng/g lipid weight) in Belgian human tissues.
CB132 and \( p,p'-\text{DDD} \) coeluting on the column used on GC-ECD.

**Quality control.** The limit of detection (LOD) was defined as 3 times the standard deviation of measured values for samples \((n = 7)\) spiked with the analyte amount that produced a signal approximately equal with three times the noise response in a blank sample. For MeSO\(_2\)-CB and MeSO\(_2\)-DDE determination, the limits of detection ranged from 0.06 to 0.10 ng/g lipid weight. Average recoveries of individual MeSO\(_2\)-CB congeners and MeSO\(_2\)-DDE from vegetable oil spiked with standards (1 ng) ranged between 84% and 99%, with a mean value of 89%. For PCB and organochlorine pesticide determination, the LOD ranged from 0.40 ng/g (CB149) to 24.6 ng/g (CB28), and the recovery ranged from 84 to 111%. The recoveries of internal standards (CB46 and CB143) in the samples ranged from 60 to 97%. No recovery correction was applied to the final results. Quality control was ensured by regular analysis of procedural blanks and of certified reference material (CRM 350, PCBs in mackerel oil; Bureau of Community Research, Geel, Belgium), for which all measurements were within the range of certified values.

All statistical analyses were completed with STATISTICA for Windows, version 5.1, from StatSoft, Inc. (Tulsa, OK, USA). Concentrations of pollutants in tissues are summarized using arithmetic means along with minimum and maximal values (Tables 2 and 3).

**Results**

The individual concentrations of 26 MeSO\(_2\)-CB congeners and 3-MeSO\(_2\)-DDE, together with the sum of MeSO\(_2\)-CBs, measured in four different tissues from 11 Belgian subjects are presented in Table 2. Individual and total concentrations of 29 PCB congeners, together with concentrations of selected organochlorine pesticides \((p,p'-\text{DDE}, p,p'-\text{DDD}, \text{and } p,p'-\text{DDT})\), are shown in Table 3. All concentrations listed in Tables 2 and 3 are expressed in nanograms per gram lipid weight, to conveniently compare them with previously reported data. Concentrations of CB18, CB28, and CB31 were below the LOD in all samples and are omitted from Table 3.

The sum of determined PCBs and \( p,p'-\text{DDE} \) (expressed per lipid weight) was similar in adipose tissue and liver from the same subject. However, higher concentrations of MeSO\(_2\)-CBs, ranging from 1.68 to 27.03 ng/g lipid weight, were found in liver compared with other tissues (Table 2). The ratios between the sum of MeSO\(_2\)-CBs and the sum of PCBs and between MeSO\(_2\)-DDE and \( p,p'-\text{DDE} \), as calculated from the individual values, were 4–28 and 2–11 times higher in liver than in adipose tissue, respectively. When comparing levels of contaminants (expressed on wet weight basis) between the tissues from the same subject, the highest concentrations were found in adipose tissue. The total concentration of MeSO\(_2\)-CBs decreased in the following order: adipose (mean, 1.30 ng/g wet weight; range, 0.25–3.62 ng/g) > liver (mean, 0.79 ng/g; range, 0.14–3.78 ng/g) > lung (mean, 0.03 ng/g; range, not detected (ND) to 0.14 ng/g) = brain (mean, 0.02 ng/g; range, ND-0.05 ng/g).

The data on chemical residues were not normally distributed (Lilliefors test), and therefore, all data were log-transformed before statistical analysis. Values below the LOD were set to zero. Pearson’s correlation coefficients between the sum of MeSO\(_2\)-CBs or MeSO\(_2\)-DDE and the sum of PCBs or DDE were not high (Tables 4 and 5) and sometimes not statistically significant, whereas they were very low for most individual MeSO\(_2\)-CBs and their corresponding PCB precursors. Significant correlation \((p < 0.05)\) was found between age and sum of PCBs in lung, adipose tissue, and liver, whereas age was correlated only with sum of MeSO\(_2\)-CBs in adipose tissue (Table 4).

The investigated tissues had characteristic profiles for the MeSO\(_2\) metabolites. In adipose, brain, and lung tissues, 4’-MeSO\(_2\)-CB87 and 4’-MeSO\(_2\)-CB101 occurred at higher concentrations than did other MeSO\(_2\)-CBs. These two congeners contributed together, on average, 55, 67, and 50% to the sum of MeSO\(_2\)-CBs in adipose, brain, and lung, respectively. In adipose tissue, the concentration of 3’-MeSO\(_2\)-CB132 was below the LOD or < 10% of the sum of MeSO\(_2\)-CBs. In contrast, 3’-MeSO\(_2\)-CB132 was the most abundant MeSO\(_2\)-CB congener in liver, contributing on average 59% to the sum of MeSO\(_2\)-CBs. In liver, the concentration of the sum of 3-MeSO\(_2\)-CBs was higher than for the sum of 4-MeSO\(_2\)-CBs, whereas in other tissues a reversed condition was observed. The ratio between the concentrations of the sum of 3-MeSO\(_2\)-CBs and the sum of 4-MeSO\(_2\)-CBs was 9.3, 0.3, 0.1, and 0.5 in liver, adipose, brain, and lung, respectively.

**Discussion**

The concentrations of MeSO\(_2\)-CB congeners and MeSO\(_2\)-DDE varied in various tissues from the subjects. Most of the lower chlorinated MeSO\(_2\)-CB congeners were not detected in human tissues, probably because of a reduced abundance of lower chlorinated PCBs in the tissues (Table 3). In contrast, congeners with four to six chlorine atoms predominated in accordance with the longer biologic half-lives of the higher chlorinated MeSO\(_2\) metabolites (Letcher et al. 2000a).

Weistrand and Norén (1997) have reported that the concentration of MeSO\(_2\)-CBs in Swedish subjects ranged from 2.0 to 9.0 ng/g lipid weight in adipose tissue and from 11.8 to 358 ng/g lipid weight in liver. The concentrations of MeSO\(_2\)-CBs are similar for adipose tissue in the Swedish and the present study, whereas the concentrations of MeSO\(_2\)-CBs in Swedish liver are higher than the levels determined in the Belgian subjects, resulting from the wider concentration range determined in the Swedish liver samples. A possible explanation might be the difference in the age of subjects in both studies (34 years for Belgian subjects and 68 years for Swedish individuals), although only low correlation coefficients between MeSO\(_2\)-CBs and age could be computed (Table 4). The difference in the diet might have an impact, as well. In addition, the PCB and \( p,p'-\text{DDE} \) levels in the Belgian subjects investigated in this study were lower than in the Swedish samples collected in the 1990s, probably in accordance with the decrease in PCB contamination during the last 10 years (Norén and Meironytė 2000).

Ellerichmann et al. (1998) determined the enantiomers of eight MeSO\(_2\)-CBs atropisomers in human liver and lung and found that the concentration of MeSO\(_2\)-CBs present in

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**Table 4.** Pearson’s correlation coefficients for certain individual and total concentrations of methyl sulfones of PCBs and DDE versus individual and total concentrations of PCBs and \( p,p'-\text{DDE} \) in different tissues from 11 subjects.

|                        | Liver          | Adipose tissue | Lung        |
|------------------------|----------------|----------------|-------------|
| MeSO\(_2\)-CB101 vs. CB101 | 0.26 (p = 0.41) | 0.55 (p = 0.08) | NC          |
| MeSO\(_2\)-CB132 vs. CB132  | 0.87**         | NC             |             |
| MeSO\(_2\)-DDE vs. \( p,p'-\text{DDE} \) | -0.02 (p = 0.95) | -0.16 (p = 0.63) | NC          |
| Sum MeSO\(_2\)-CBs vs. sum PCBs | 0.52 (p = 0.10) | 0.79**         | 0.36 (p = 0.28) |
| MeSO\(_2\)-DDE vs. \( p,p'-\text{DDE} \) | 0.69*          | 0.67*          | NC          |
| Sum MeSO\(_2\)-CBs vs. age  | 0.32 (p = 0.34) | 0.65*          | 0.31 (p = 0.35) |
| Sum PCBs vs. age          | 0.75**         | 0.81**         | 0.58*       |

NC, not computed because most values were below the LOD. MeSO\(_2\)-CB is the sum of corresponding 3-MeSO\(_2\)-CB and 4-MeSO\(_2\)-CB. All data were log-transformed before statistical analysis.

\( * p < 0.05 \) \( ** p < 0.01 \)
lung was substantially lower than in liver tissue. This result is in accordance with the present study, where MeSO2-CBs and MeSO2-DDE are also preferentially stored in the liver relative to other tissues. Calculated on a wet-weight basis, the concentrations of MeSO2-CBs in the lung were 1–2 orders of magnitude lower than those in adipose or liver, because of a much lower lipid percentage (Ellerichmann et al. 1998). In an early investigation (Haraguchi et al. 1986), MeSO2-CBs concentrations in lung and adipose tissue from a patient who died from causes unrelated to the Yusho accident are similar to those found in the present study. However, in the Yusho patient, the highest concentration of MeSO2-CBs was found in lung (15.9 ng/g wet weight). The Yusho patient had ingested rice oil contaminated with MeSO2-CB is the sum of corresponding 3-MeSO2-CB and 4-MeSO2-CB. All data were log-transformed before statistical analysis. Table 5. Pearson’s correlation coefficients for methyl sulfones of PCBs and DDE versus total concentrations of PCBs and p,p’-DDE in different tissues from 11 subjects. **P < 0.01. *P < 0.05. MeSO2-CB is the sum of corresponding 3-MeSO2-CB and 4-MeSO2-CB. All data were log-transformed before statistical analysis.

For monitoring of MeSO2-CB residues in human tissues, blood and milk were more often investigated (Newsome and Davies 1996; Norén et al. 1996). It was reported that the mean concentration for the sum of MeSO2-CBs was 1.7 ng/g lipid in Canadian human milk, and the major congeners were 3′-MeSO2-CB101, 4′-MeSO2-CB87, and 4′-MeSO2-CB151 (Newsome and Davies 1996). In Swedish human milk, the concentration of MeSO2-CBs decreased from 9 to 2 ng/g lipids between 1972 and 1992, and the concentrations of 4-MeSO2-CBs were higher than the corresponding 3-MeSO2-CBs, with the major congeners being 4′-MeSO2-CB87 and 4-MeSO2-CB149 (Norén et al. 1996). Norén et al. (1999) reported that the concentration of the sum of MeSO2-CBs in Swedish human plasma ranged from 1 to 5 ng/g lipids, and that 4-MeSO2-CB149, 4′-MeSO2-CB87, and 4′-MeSO2-CB101 were the dominant congeners. These congener profiles seem to be similar to those in the adipose tissue investigated in the present study, although we did not determine the presence of 4′-MeSO2-CB151.

3′-MeSO2-CB132 is the most abundant MeSO2-CB congener found in liver, contributing an average of 59% to the sum of MeSO2-CBs (Figure 1). Similar results were found in previous investigations (Weistrand and Norén 1997, 1998), where 3′-MeSO2-CB132 was present in higher concentration than other MeSO2 metabolites in Swedish human liver, whereas 4′-MeSO2-CB87 and 4-MeSO2-CB149 were the predominant MeSO2-CBs in adipose samples. In the present study, the concentration of the sum of 3-MeSO2-CBs in liver was higher than the sum of 4-MeSO2-CBs, whereas in other tissues a reversed condition was observed. A specific affinity for 3-MeSO2-CBs in the liver has been observed in gray seals and otters (Bergman et al. 1994), whereas a specific retention of 4-MeSO2-CBs has been observed in the lungs of rats and mice (Bergman et al. 1979; Haraguchi et al. 1999). This phenomenon indicates a different binding affinity (probably also species dependent) of 3-MeSO2-CB and 4-MeSO2-CB metabolites in various tissues (Haraguchi et al. 1999).

The profiles of MeSO2-CB congeners in human tissues differ from those obtained from wild animals (Bergman et al. 1994). In muscle or blubber of wildlife (otter, mink, and gray seal) from Sweden, 3′-MeSO2-CB101 was the predominant MeSO2-CB congener, although 4′-MeSO2-CB101 was also found at high concentrations (Bergman et al. 1994). Letcher et al. (1995a, 1995b) reported that the concentration of total MeSO2-CBs in polar bear liver was 4–8-fold higher than in fat, with 3′- and 4′-MeSO2-CB87, 3′- and 4′-MeSO2-CB101, and 4-MeSO2-CB149 congeners accounting for approximately 53% of the sum of MeSO2-CBs. Both 3′- and 4′-MeSO2-CB101 were found at the highest concentrations in blubber of harbor porpoises, followed by 3′- and 4′-MeSO2-CB87, 3′- and 4′-MeSO2-CB101, and 3′- and 4-MeSO2-CB149 (Karlson et al. 2000). It seems that in these species, the bioaccumulation/bioformation efficiency is less selective for 3′- and 4-MeSO2-CB metabolites.

In the present study, it is not possible to clearly determine the relative roles of bioaccumulation versus bioformation of MeSO2 metabolites, but it is useful to indicate that...
MeSO2-DDE standards were unavailable. The reason why there is such poor or no correlation between wildlife and humans could be because of a very different diet. Because of a very different diet. The relative importance of bioaccumulation between wildlife and humans could be because of a very different diet. Most of the remaining congeners (3- and 4-MeSO2-CB31, 3´- and 4´-MeSO2-CB49, 3- and 4-MeSO2-CB110 and 3-MeSO2-CB149) were likely bioaccumulated. The reason why patterns of MeSO2-CBs differ between wildlife and humans could be because of the relative importance of bioaccumulation may be higher in some wildlife species and because of a very different diet.

MeSO2-CBs, MeSO2-DDE, and their precursor compounds (PCBs and p,p'-DDE) are all lipophilic contaminants, but their bioaccumulation efficiency is not similar. MeSO2-CBs and MeSO2-DDE are selectively retained in liver tissues because of specific protein binding (Brandt and Bergman 1987). This phenomenon was also observed in the present study. In paired samples of human adipose tissue and liver, the concentrations of PCBs and DDE were similar on the lipid weight basis, but the concentrations of methylsulfonyl metabolites were different. The average ratios of the sum MeSO2-CBs to the sum PCBs were 1/306 and 1/39 in adipose tissue and liver, respectively. This phenomenon was observed in the present study. In paired samples of human adipose tissue and liver, the concentrations of PCBs and DDE were similar on the lipid weight basis, but the concentrations of methylsulfonyl metabolites were different. The average ratios of the sum MeSO2-CBs to the sum PCBs were 1/306 and 1/39 in adipose tissue and liver, respectively.

**In conclusion, the present results show that MeSO2-CB congeners have a different distribution, both as concentration and as profiles, in human tissues. Further studies are needed to reveal details of their mechanisms and their selective protein-binding affinity in different tissues.**

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