



# Body weight loss increases plasma and adipose tissue concentrations of potentially toxic pollutants in obese individuals

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**BACKGROUND:** While there appears to be a consensus among scientists and clinicians that body weight loss reduces the risk of several chronic diseases, these apparently favourable effects should be balanced against any potentially harmful side effect of weight loss. In this regard, weight loss has been shown to produce an increase in blood concentration of potentially toxic organochlorine pollutants in animals that can cause prejudice to health, but human data are lacking.

**METHODS:** Thirty-nine obese individuals were subjected to a hypocaloric diet during 15 weeks. Blood and subcutaneous adipose tissue samples were analysed before and after treatment for 26 organochlorine compounds. A control group consisting of 57 women of similar mean age was also formed in order to compare plasma concentrations.

**RESULTS:** Organochlorine pollutants were found in every subject and all 19 compounds detected had their plasma concentration increased following treatment (mean body weight loss 9.5 kg), 15 of which were statistically significant. When compared with a control group, five compounds increased significantly. These observations persisted after an 18 week low-fat diet/exercise program follow-up. Increases were correlated with body weight loss ( $-0.3 \geq r \geq -0.6, P < 0.05$ ) and adipose tissue analyses yielded similar results, as their concentration of organochlorine compounds increased following treatment.

**CONCLUSION:** Body weight loss increases plasma and subcutaneous adipose tissue concentrations of organochlorine pesticides and PCBs in obese subjects. These results raise concerns about an undesired and potentially harmful side effect of weight loss in some obese patients who seem to be at greater risk of health problems than leaner subjects since they show higher organochlorine body burden.

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## Introduction

The years following the Second World War saw the mass production of cheap synthetic petrochemical compounds characterized by their high resistance to degradation. These compounds were used as highly effective pesticides, dielectric fluids, fire retardants and were included in ink, plastic and rubber mixtures. The halogenated organic compounds were considered to be the most potentially toxic, among which the chlorinated compounds (named organochlorines) are the most commonly found in living organisms. Up until the 1970s, when they were banned, organochlorine pesticides and polychlorinated biphenyls (PCBs) were extensively used throughout the world and were released in the environment in very large amounts. Owing to their resistance to enzymatic degradation

and to their lipophilic properties, these products are particularly persistent in living organisms and accumulate in their fat over years. They can therefore bioaccumulate through food absorption so that the greatest concentrations are found in species that occupy the highest position in the food chain. Nowadays, organochlorines are found in virtually every person on the planet and banned compounds are still synthesized in the Western world for use in developing countries.

The realization that these compounds could be unexpectedly toxic as well as uncontrollable was first made by Carson.<sup>1</sup> Since then, several organochlorine compounds have been characterized as oestrogenic and hormone-disrupters. For instance, beta-hexachlorocyclohexane ( $\beta$ -HCH) increases the amount of progesterone receptors in cancerous cells MCF-7 derived from the human breast.<sup>2</sup> It was also demonstrated that this compound could act as a cancer promoter in increasing the growth rate of this line of tumor cells.<sup>3</sup> Furthermore,  $\beta$ -HCH was found in greater concentrations in the adipose tissue of women affected by breast cancer than in healthy controls.<sup>4,5</sup>

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Other organochlorines such as dichlorodiphenyl dichloroethene (DDE), the main metabolite of the pesticide dichlorodiphenyl trichloroethane (DDT), is also considered as a hormone-disrupter. This product was described as a potent androgen receptor antagonist and its presence in the environment is considered as a possible explanation for the reported increased incidence of human male reproductive tract abnormalities such as a decreased sperm count<sup>6</sup> and an increased hypospadias and testicular cancer incidence.<sup>7,8</sup> It was reported that DDE interferes with androgen binding to the androgen receptor and inhibits androgen-induced transcriptional activity and androgen action in rats.<sup>9</sup>

Moreover, PCBs at environmental background concentration were found to mainly affect the foetus in development, probably through a hormone-disrupting process. One of the best known studies on the impact of exposure to PCBs was conducted by Fein *et al.*<sup>10</sup> They reported that infants born to mothers who ate an average of two to three PCB-contaminated Lake Michigan trout or salmon per month were lighter and had a smaller head circumference than a control group even when taking into account 37 potential confounding variables. Four years later, exposed children still suffered from the adverse effects of their exposure since they presented a poorer short-term memory compared with a control group.<sup>11</sup>

Since organochlorine compounds are stored in fat, it has been suggested that body fat loss, in reducing the storage capacity, could result in increased organ and blood concentrations which could induce adverse effects.<sup>12</sup> Ohmiya and Nakai<sup>13</sup> confirmed this hypothesis when they starved mice after treating them with a load of <sup>14</sup>C-DDT. They found that blood, adipose tissue, heart, lung, kidney, liver, spleen and brain concentrations of DDT-related compounds were increased by about 2- (spleen) to 7-fold (brain). Later, the demonstration that the increase in concentration caused by weight loss could lead to oestrogenic effects was performed by Bigsby *et al.*<sup>14</sup> who noticed a greater uterine weight in fasted  $\beta$ -HCH-loaded mice than in fed mice. It was concluded that the increased uterine weight was due both to cell hyperplasia and hypertrophy. Furthermore, while some organochlorine compounds showed immunotoxic effects in animals,<sup>15,16</sup> they have also been found to be immunosuppressive in environmental doses in humans to the same extent as weight loss.<sup>17</sup>

In humans, several studies have suggested that weight loss may cause prejudice to health. Scanga *et al.*<sup>18</sup> demonstrated that weight loss could weaken the immune system by decreasing the amount of leukocytes and lymphocytes and by suppressing natural killer cell activity. Several epidemiological studies have also reported associations between weight loss and increased mortality rate.<sup>19,20</sup> Since body weight loss is considered worldwide as a necessity to counteract the obesity epidemic prevailing in many countries, its potential impact on the release of toxic compounds

is a source of concern. The aim of this study was thus to determine whether body weight loss increases plasma and adipose tissue concentrations of lipophilic and potentially toxic organochlorine compounds in humans. In addition, we examined whether obese subjects had greater plasma concentrations of these compounds than lean controls.

## Methods

### Subjects and protocol

Thirty-nine obese individuals (21 premenopausal women and 18 men, see Table 1) whose BMI ranged between 30 and 47 kg/m<sup>2</sup> were subjected to a two-phase treatment which took place from 1995 to 1997. In the first phase, subjects followed a non-macronutrient specific energy-restricted diet of 700 kcal over a period of 15 weeks. The diet was based on a daily energy expenditure (DEE) estimated from resting metabolic rate measurement to which an activity factor of 1.4 was multiplied. The energy intake was then calculated by subtracting 700 kcal from DEE. A 3 day dietary record was also used to assess energy and macronutrient intake of subjects. In order to facilitate weight loss and to encourage compliance, 32 subjects underwent drug therapy consisting of a daily dose of 60 mg of fenfluramine while the seven other subjects formed a placebo group.

Seventeen subjects participated in the second phase of treatment which consisted of a physical activity and low-fat diet programme from which 30% of total energy intake came from fat, 53% from carbohydrates and 17% from proteins. This treatment was maintained until subjects showed resistance to losing further body weight, which occurred after a mean supervision period of 18 additional weeks.<sup>21</sup>

### Control group

A control group of similar mean age was formed in order to compare obese and lean subjects. This group consisted of 57 normal-weight women (Table 1) who were tested between 1994 and 1997 for plasma concentrations of the above referenced compounds using the same procedure as described.

**Table 1** Characteristics of the subjects

	Obese (n = 39)	Lean (n = 57)
Age (y)	43.4 ± 4.6	42.8 ± 3.8
BMI (kg/m <sup>2</sup> )		
Before phase I	35.2 ± 3.5	23.9 ± 4.8
After phase I	31.8 ± 3.6	
After phase II	29.7 ± 2.3	

Values are means ± s.d.

### Body composition measurements

The hydrostatic weighing technique was used to measure body density from which percentage body fat was estimated using the Siri equation.<sup>22</sup> This measurement also required the determination of the pulmonary residual volume, which was done by following the procedures described by Meneely and Kaltreider.<sup>23</sup> Total body fat mass was calculated from body weight and percentage body fat, and fat-free mass was considered as the difference between body weight and fat mass.

### Chemical analysis

Fourteen PCB congeners (IUPAC nos. 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183 and 187) and 11 chlorinated pesticides (aldrin, *p,p'*-DDT, *p,p'*-DDE,  $\beta$ -HCH,  $\alpha$ -chlordane,  $\gamma$ -chlordane, oxychlordane, *cis*-nonachlor, *trans*-nonachlor, hexachlorobenzene and mirex) were determined in plasma and adipose tissue samples in fasted subjects. Blood samples were taken before and following phase one as well as following phase two, whereas subcutaneous femoral and abdominal adipose tissue biopsies were performed before and after phase one. Blood sample analyses were done as follows. Blood plasma (2 ml) was extracted, cleaned up on Florisil columns, taken to a final volume of 100  $\mu$ l and analysed on an HP-5890 series II gas chromatograph with dual-capillary columns and dual <sup>63</sup>Ni electron detectors. Peaks were identified by their relative retention times obtained on the two columns using a computer program developed by the Québec Toxicology Center. Total and free cholesterol (TC and FC), triglycerides (TG) and phospholipids (PL) were also individually measured using enzymatic methods on a Technicon automatic analyzer (RA-500) with the following test packs: Randox for TG and TC; BMC for FC and Wako for PL. Plasma total lipids were then calculated using the following summation method as recommended by Patterson *et al.*<sup>24</sup>

$$\text{Total lipids} = 1.677(\text{TC} - \text{FC}) + \text{FC} + \text{TG} + \text{PL}$$

Adipose tissue samples were first spiked with the internal standard (PCB congener no.198), homogenized in hexane : acetone (2 : 1, v/v) and the resulting organic phase was washed with water to remove the bulk of the acetone. An aliquot of the hexane extract was used for lipid determination by gravimetry and the rest of the extract was defatted with concentrated sulphuric acid. The defatted hexane was successively washed with water and aqueous potassium hydroxide prior to filtration through anhydrous sodium sulphate. The filtrate was then concentrated and cleaned up by chromatography on an acidic silica gel column and a deactivated (0.5%) Florisil column. Organochlorines were eluted from the columns using methylene chloride : hexane (25 : 75, v/v) and analysed on a HP-5890 gas chromatograph equipped with dual capillary columns (Ultra-1 and Ultra-2) and dual <sup>63</sup>Ni electron detectors. Depending on the lipid content and the available quantity of tissues, detection limits varied

from 6.4 to 43  $\mu$ g/kg and from 0.02 to 0.3  $\mu$ g/l in adipose tissue and plasma, respectively.

### Statistical analyses

Student's paired *t*-test was used to evaluate the effect of phase I of treatment on plasma organochlorines concentrations when the data's distribution curve was normal or could be normalized using appropriate transformation. Wilcoxon's signed-rank test was used when the curve could not be normalized. The test was also used with small samples such as the comparison of adipose tissue organochlorine concentrations following phase I (nine femoral and 10 abdominal samples) and to assess the effect of the second phase of treatment on plasma organochlorine concentrations (17 samples). One-way ANOVA was used to compare obese patients with lean controls. Pearson's correlation coefficient (with normal or normalized distribution) and Spearman's rho (with small sample and non-normal distribution) were utilized to assess the degree of relationship between variables. Non-detectable results were given half the detection limit for statistical considerations.

## Results

### Plasma concentrations

As expected, organochlorine pollutants were found both in adipose tissue and plasma of every obese and lean subject.

All detected compounds (19) showed a trend towards increased plasma concentration following the initial phase of the weight-reducing programme which induced an average 9.5 kg body weight loss. As recently reported, most of the weight lost was explained by body fat loss.<sup>21</sup> Increases were statistically significant for 15 compounds, whether expressed on a plasma volume (mean of increases 16.4%) or plasma lipid weight basis (mean of increases 18.8%, see Table 2). Consequently, the total organochlorine concentration (being the sum of all detected compounds) was also increased by weight loss (Figure 1). These increased concentrations were negatively correlated with changes in body weight, fat mass and BMI in phase I (Table 3). Although correlations were stronger in the second phase ( $-0.51 \geq r \geq -0.71$ ,  $P < 0.05$ ), this part of treatment did not cause significant additional changes in plasma concentrations (mean additional body weight loss 4.0 kg; see Table 2). It is noteworthy to emphasize that the increases observed following phase I persisted after phase II of treatment. An inverse relationship between the change in plasma concentration per kilogramme of fat lost and the initial body weight was, however, noticed for seven compounds ( $-0.34 \geq r \geq -0.48$ ,  $P < 0.05$ ).

### Adipose tissue concentrations

As in plasma, adipose tissue concentrations of organochlorines were elevated following the first phase of treatment. Statistically significant increases were

**Table 2** Plasma organochlorine concentrations before and after each phase of treatment

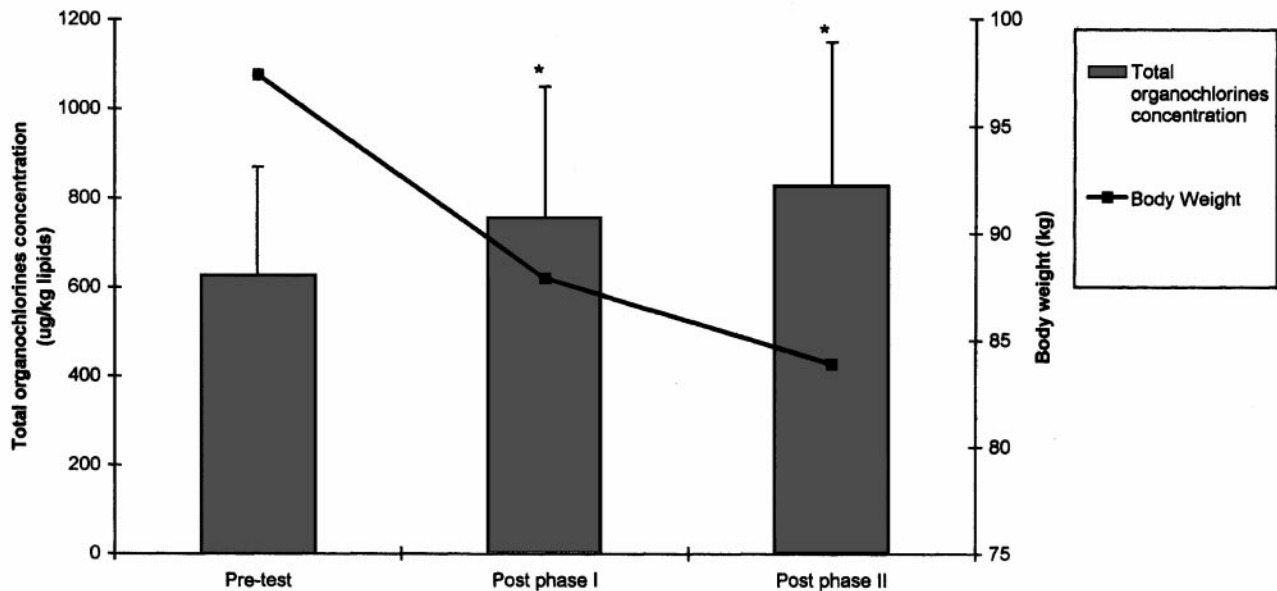
Compounds	Phase I (n = 39)			Phase II (n = 17)	
	Pre (µg/l)	Post (µg/l)	Δ Phase I (%)	Post (µg/l)	Δ Phase II (%)
β-HCH	0.117 ± 0.11	0.138 ± 0.143	17.9**	0.166 ± 0.22	20.3
p,p'-DDE	2.45 ± 1.4	2.81 ± 1.7	14.7 <sup>†</sup>	2.72 ± 1.7	-3.2
p,p'-DDT	0.057 ± 0.04	0.063 ± 0.05	10.5*	0.040 ± 0.03	-36.5
HCB	0.133 ± 0.07	0.151 ± 0.08	13.5**	0.148 ± 0.04	-2.0
Mirex	0.021 ± 0.015	0.021 ± 0.01	0	0.025 ± 0.02	19.0
Oxychlorane	0.059 ± 0.03	0.067 ± 0.03	13.6 <sup>†</sup>	0.068 ± 0.03	1.5
Trans-nonachlor	0.079 ± 0.04	0.088 ± 0.04	11.4**	0.091 ± 0.04	3.4
Aroclor 1260	2.79 ± 1.2	3.18 ± 1.3	14.0 <sup>†</sup>	3.33 ± 1.4	4.7
PCB 28	0.024 ± 0.02	0.031 ± 0.02	29.2**	0.030 ± 0.02	-3.2
PCB 99	0.064 ± 0.03	0.075 ± 0.04	17.2 <sup>†</sup>	0.078 ± 0.05	4.0
PCB 118	0.102 ± 0.05	0.120 ± 0.06	17.6 <sup>†</sup>	0.114 ± 0.07	5.0
PCB 138	0.228 ± 0.10	0.258 ± 0.12	13.2 <sup>†</sup>	0.276 ± 0.13	15.0
PCB 153	0.309 ± 0.12	0.356 ± 0.14	15.2 <sup>†</sup>	0.367 ± 0.15	3.1
PCB 156	0.046 ± 0.02	0.056 ± 0.03	21.7**	0.053 ± 0.02	-5.3
PCB 170	0.063 ± 0.03	0.073 ± 0.03	15.9 <sup>†</sup>	0.078 ± 0.03	6.8
PCB 180	0.160 ± 0.06	0.185 ± 0.07	15.6 <sup>†</sup>	0.191 ± 0.06	3.2
PCB 187	0.044 ± 0.01	0.051 ± 0.02	15.9 <sup>†</sup>	0.053 ± 0.02	3.9

Values are means ± s.d.

Phase II did not induce additional significant change.

Δ Values are determined as the differences between the data shown above.

\*P<0.05; \*\*P<0.01; <sup>†</sup>P<0.001.



**Figure 1** Effect of treatment on body weight and total organochlorines concentration (being the sum of all detected compounds). \*P<0.0001 compared with the pre-test.

observed in both abdominal (mean of increases 18.3%) and femoral (mean of increases 19.0%) subcutaneous adipose tissue in 12 and eight out of 14 detected compounds, respectively (Table 4).

No significant associations were found between variations in adipose tissue concentrations and changes in body weight, fat mass or BMI nor were related initial anthropometric data with organochlorine levels.

#### Comparison with non-obese controls

A greater plasma HCB and PCB 118 concentration and a lower PCB 170 concentration were found when comparing obese and lean subjects before weight loss. However, PCB 118, 138, 156, β-HCH and HCB plasma concentrations were significantly higher in reduced-obese subjects than in controls following

phase I of treatment (Figure 2) with a general trend toward increased concentrations for other detected compounds (results not shown).

## Discussion

Results of the present study confirm what had previously been reported in animal models. Indeed, body weight loss, and presumably body fat loss, increases the plasma as well as the adipose tissue concentrations of lipophilic and potentially toxic organochlorine pollutants in humans. The hypothesis is reinforced by the highly significant correlations obtained between body weight loss, body fat loss and changes in the compounds plasma concentrations. It is there-

**Table 3** Correlations between  $\Delta$ body weight,  $\Delta$ fat mass, and residuals of  $\Delta$ organochlorine plasma concentrations adjusted for plasma lipids in phase I of treatment ( $n = 39$ )

Compounds	Correlations ( <i>r</i> )		
	$\Delta$ Body weight	$\Delta$ Fat mass	$\Delta$ Body mass index
$\Delta\beta$ -HCH	NS	-0.37*	NS
$\Delta p,p'$ -DDE	-0.43 <sup>†</sup>	-0.45 <sup>†</sup>	-0.43 <sup>†</sup>
$\Delta$ HCB	NS	NS	-0.31*
$\Delta$ Aroclor 1260	-0.44 <sup>†</sup>	-0.43 <sup>†</sup>	NS
$\Delta$ PCB 99	-0.47 <sup>†</sup>	-0.39*	-0.50 <sup>†</sup>
$\Delta$ PCB 118	-0.40*	-0.39*	-0.41 <sup>†</sup>
$\Delta$ PCB 138	-0.42 <sup>†</sup>	-0.42 <sup>†</sup>	-0.38*
$\Delta$ PCB 153	-0.45 <sup>†</sup>	-0.43 <sup>†</sup>	-0.38*
$\Delta$ PCB 170	-0.32*	NS	NS
$\Delta$ PCB 180	-0.36*	-0.35*	NS

\* $P < 0.05$ ; <sup>†</sup> $P < 0.01$ .  
NS: statistically non-significant.

fore suggested that pollutants could be released from the adipose tissue compartment into the blood stream along with mobilized lipids as subjects lost weight. The volume of dilution (that is the organism's overall fat content) being reduced through weight loss, and since organochlorines are hardly eliminated, the overall concentration of these compounds would be increased in every fatty tissue to reach a new equilibrium.

Such results allow us to infer that the animal model data described by Ohmiya and Nakai<sup>13</sup> may be relevant to humans. Consequently, elevated concentrations of organochlorine pollutants in a human's blood stream through weight loss and decreased volume of distribution would cause a rise of these compounds in the heart, lungs, kidneys, liver and spleen as well as brain, which may in turn increase the risks of health problems previously described. This could provide a potential explanation for the mechanism underlying the relation between weight loss and an impaired immune system observed by Scanga *et al*<sup>18</sup> and Stallone *et al*.<sup>25</sup> Accordingly, it could provide an

explanation of the association of weight loss with an increased mortality rate.<sup>19,20</sup> However, Doucet *et al*<sup>21</sup> have demonstrated that reduced-obese subjects having healthy food habits and exercising regularly present a normalized metabolic profile despite anthropometric data categorizing them as being at risk for developing chronic diseases. Taken together, those results suggest that, in some cases, it could be preferable to moderate body weight loss although further research will need to be done before drawing such conclusions.

A lower initial fat mass was related with a higher elevation in the plasma concentration per kilogramme of fat lost. This suggests that for a certain fat mass loss, less obese people release a greater amount of lipophilic pollutants in to their blood stream.

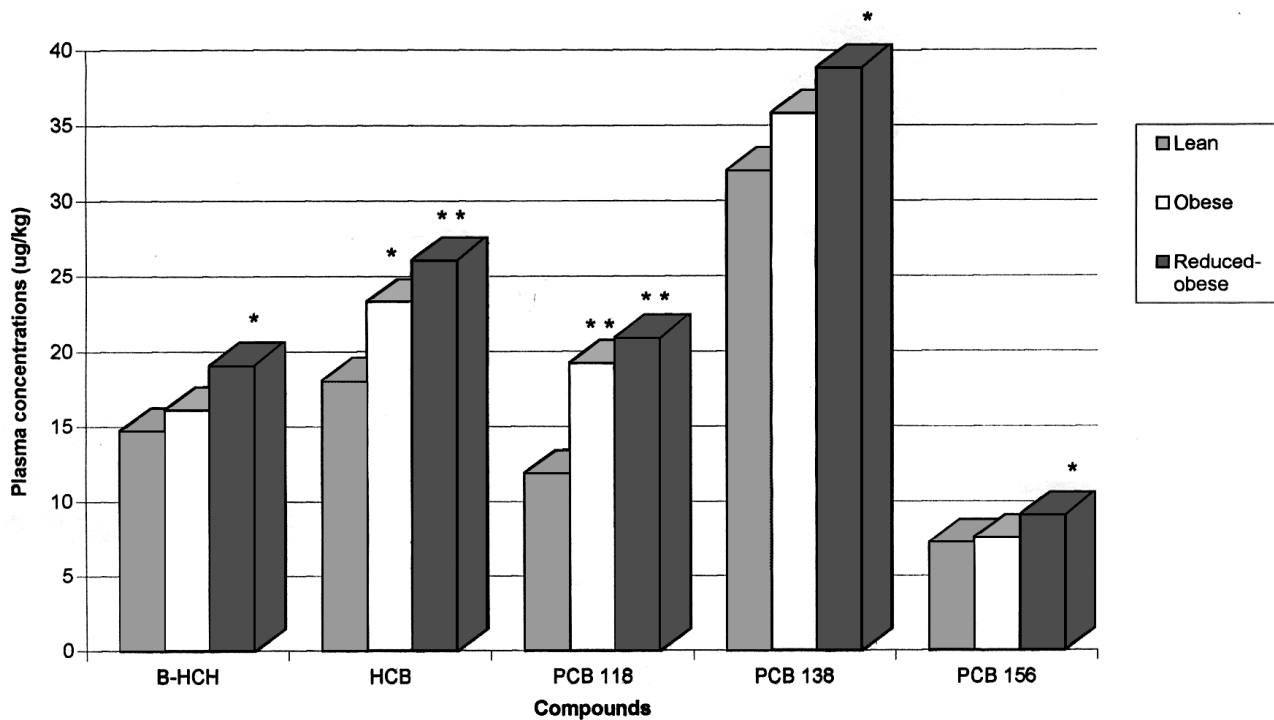
When compared with a lean control group for the plasma concentrations of organochlorines, the obese group initially showed virtually no significant differences and did not show any noticeable trend. However, after treatment five compounds were found in higher concentration in the reduced-obese group with a general trend towards significance for the other compounds. These results may have two major implications. Firstly, individuals having a greater fat mass and therefore an increased storage potential exhibit a total concentration of organochlorines that is higher than in lean subjects. Secondly, obese patients may be more prone to elevating their plasma concentration of organochlorines through body weight loss that could potentially put their health at risk. Thus, adipose tissue could be regarded as having a role of protection by keeping lipophilic toxicants away from organs.

In summary, body weight and fat losses in obese subjects induced an increase in plasma and adipose tissue concentrations of lipophilic and potentially toxic organochlorine pollutants. Both body weight and fat losses were correlated with the magnitude of the changes in plasma pollutant concentrations. These results could possibly explain in part the controversial association between weight loss and increased mor-

**Table 4** Mean subcutaneous abdominal and femoral adipose tissue concentrations before and after phase I of treatment

Compounds	Abdominal ( $n = 10$ )			Femoral ( $n = 9$ )		
	Before ( $\mu\text{g}/\text{kg}$ )	After ( $\mu\text{g}/\text{kg}$ )	<i>P</i>	Before ( $\mu\text{g}/\text{kg}$ )	After ( $\mu\text{g}/\text{kg}$ )	<i>P</i>
$\beta$ -HCH	34.25 $\pm$ 43.2	41.95 $\pm$ 50.3	0.009	44.72 $\pm$ 48.0	46.61 $\pm$ 50.5	NS
$p,p'$ -DDE	512.2 $\pm$ 284	628.2 $\pm$ 430	0.003	554.9 $\pm$ 275	652.3 $\pm$ 359	NS
$p,p'$ -DDT	23.45 $\pm$ 12.6	25.67 $\pm$ 9.83	NS	30.11 $\pm$ 12.9	38.78 $\pm$ 21.2	NS
HCB	23.40 $\pm$ 3.17	27.5 $\pm$ 6.72	0.035	27.22 $\pm$ 7.74	31.67 $\pm$ 9.10	NS
Oxychlorodane	22.40 $\pm$ 5.30	26.2 $\pm$ 10.0	0.027	24.72 $\pm$ 10.0	30.33 $\pm$ 10.2	0.020
Trans-nonachlor	31.80 $\pm$ 8.24	36.90 $\pm$ 13.5	0.050	34.39 $\pm$ 13.8	41.89 $\pm$ 18.8	NS
Aroclor 1260	815 $\pm$ 500	979 $\pm$ 541	0.002	783 $\pm$ 144	927 $\pm$ 239	0.027
PCB 118	24.20 $\pm$ 22.2	26.95 $\pm$ 20.8	0.008	19.44 $\pm$ 6.31	24.00 $\pm$ 5.10	0.035
PCB 138	70.50 $\pm$ 47.9	82.5 $\pm$ 48.9	0.001	63.11 $\pm$ 10.7	74.44 $\pm$ 16.8	0.027
PCB 153	86.80 $\pm$ 51.4	103.90 $\pm$ 52.4	0.002	87.11 $\pm$ 17.2	103.2 $\pm$ 29.0	0.027
PCB 156	14.91 $\pm$ 9.02	18.70 $\pm$ 9.96	0.003	15.28 $\pm$ 6.08	17.77 $\pm$ 7.34	NS
PCB 170	19.30 $\pm$ 8.22	23.65 $\pm$ 9.94	0.009	20.17 $\pm$ 7.28	24.00 $\pm$ 8.05	0.023
PCB 180	45.50 $\pm$ 14.4	55.50 $\pm$ 18.58	0.001	49.44 $\pm$ 13.0	57.56 $\pm$ 19.0	0.039
PCB 187	17.50 $\pm$ 7.11	19.85 $\pm$ 8.29	NS	17.5 $\pm$ 6.18	21.67 $\pm$ 7.89	0.025

Values are means  $\pm$  s.d.  
Mean of increases were 18.3% in abdominal tissue and 19.0% in femoral tissue.  
NS: statistically non-significant.



**Figure 2** Plasma concentrations of organochlorine compounds in obese subjects tested before and following phase I and in their lean counterparts. \* $P < 0.05$ ; \*\* $P < 0.001$ ; Degree of significance is calculated in comparison with lean subjects.

tality rates. Further studies are needed in order to assess to what extent health complications and carcinomas could be triggered by weight loss through such an increase in plasma organochlorine concentrations. Studies should be designed in order to enable clinicians to balance potentially harmful effects of body weight loss with the favourable ones in order to prescribe their patients a safe amount of weight to lose.

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