Appendix E

NZ 2378-TCDD Toxicokinetic Model

The New Zealand toxicokinetic model provides an *initial estimate* of previous 2378-TCDD exposures in New Zealand. It also estimates how previous non-background exposures may influence present day 2378-TCDD blood lipid concentrations. The model is based on a number of assumptions, including historical levels of 2378-TCDD in the food chain and age-dependent profiles of typical food intakes, body composition and elimination of 2378-TCDD. Uncertainties within each of these parameters impact on the results generated. Thus, **extreme care** is needed when using the model to predict actual population exposures. Further refining of the assumptions may reduce these uncertainties, but this is beyond the scope of the initial assessment model.

Model overview

The toxicokinetic model is presented in Microsoft Excel spreadsheets. It predicts accumulative 2378-TCDD body and total 2378-TCDD concentration per kilogram of body lipid for the general population. Separate models were developed for the New Zealand female and male populations to account for variations in body composition and intake rate. [As the same algorithmic procedures are used in both models, we refer to 'the model' (singular) throughout this document].

The model predicts the 2378-TCDD body burden for New Zealanders aged between 15 and 64 years in the year 2000, based upon an assumed dietary 'background intake' function and changing body composition and dietary intakes over an individual's lifetime.

Dioxin body burdens are calculated on a year-by-year basis, accounting for variations in food (calorific) intake, body weight and body fat. Profiles of male and female body compositions and dietary intakes are constructed for 'typical' New Zealanders aged between 1 and 64 years. These profiles are used to predict typical 2378-TCDD intakes based on assumed calorific dietary consumption, 2378-TCDD half-life in the body (based on total body fat) and the dilution of total 2378-TCDD body burden in total body fat.

The 'background intake' function estimates relative changes in the concentration of 2378-TCDD in the New Zealand diet between 1937 and the year 2000. The background intake function focuses on picograms of 2378-TCDD per day, per megajoule of food ingested. The model assumes that the body absorbs all of the 2378-TCDD ingested (100%). Using any other absorption rate would proportionally increase the 2378-TCDD concentration per megajoule ingested by the inverse of that absorption rate (ie 1 / 2378-TCDD absorption rate).

The background intake function was calibrated separately for females and males, using gender and age-specific 2378-TCDD blood lipid concentrations from the 1997 *Ministry for the Environment* organochlorines blood serum survey. Background intake function parameters

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were optimised using a JAVA software program to best match the observed 2378-TCDD blood serum concentrations.

Age groups in the model correspond to those in the *Ministry for the Environment* (MfE) blood serum study to allow calibration of the model. In order to calibrate the model with the MfE blood serum results, we assumed that the observed 2378-TCDD blood lipid concentrations reflect the average 2378-TCDD concentration in the total body lipid, as predicted by the toxicokinetic model.

In addition to typical background population exposures, the model estimates the likely effect of non-background 2378-TCDD intakes on 2378-TCDD blood lipid concentrations in the year 2000. The model allows additional 2378-TCDD intakes to be defined for a particular year or range of years. Additional intakes are quantified in terms of increased dioxin intakes in relation to an individual's age-dependent dietary intake or body weight, or as a uniform increase in dioxin intakes regardless of an individual's dietary intake or body parameters.

Model algorithms

In each gender-specific model, 2378-TCDD intakes and elimination rates are simulated for fifty virtual 'individuals.' The 2378-TCDD body burdens of each 'individual' are modelled on a year-by-year basis, taking into account age and time-dependent variations in 2378-TCDD intake rates, elimination rates and dilution in the body. Each 'individual' represents a typical New Zealand male or female aged between 15 and 64 years in the year 2000. Each 'individual' is separated by one year.

A gender-specific profile describing typical dietary intakes, body weight and percentage total body fat over an individual's lifecycle was constructed using national and international data. Each individual is assumed to follow the same life-history regarding dietary energy intakes and body composition. An individual's body and intake characteristics are assumed to be constant over each year modelled.

Elements in the calculation process are presented in Figure 1. There are three major elements used to estimate 2378-TCDD body burden at the end of the simulated year:

1. Estimated amount of 2378-TCDD in the individual's body at the end of the previous year.

2. Elimination rate of 2378-TCDD, defined in terms of a half-life and assumed to be a function of the total percentage lipid content of the body.

3. Intake rate of 2378-TCDD associated with consuming contaminated food (and any additional exposures defined by the user).

Figure 1: Components in the model calculation process
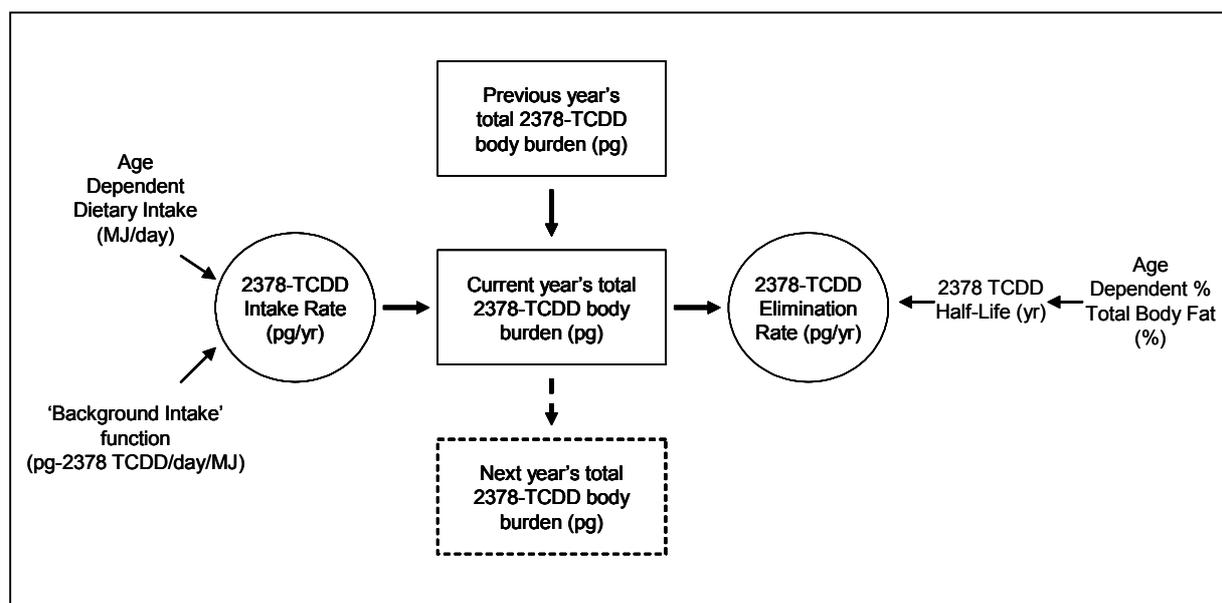
The rate of change of 2378-TCDD in the body is described as a linear first order differential equation:

$$\frac{dA_{TCDD}(t)}{dt} = I_{TCDD}(t) - k(t)A_{TCDD}(t)$$

where $A_{TCDD}(t)$ is the total amount of 2378-TCDD present in the body at year 't'. The intake rate of 2378-TCDD during the year 't' is defined as $I_{TCDD}(t)$, with units in picograms per year. The intake rate is the combination of both background intake and additional intakes. $k(t)$ is the elimination rate of 2378-TCDD for the year 't' ($year^{-1}$).

Solving this equation, and accounting for the estimated amount of 2378-TCDD already accumulated in the body from previous years, concentration levels at the end of each year can be calculated using:

$$A_{TCDD}(t) = (A_{TCDD}(t-1) + I_{TCDD}(t)/k(t))e^k - I_{TCDD}(t)/k(t)$$

The model assumes that the concentration of 2378-TCDD is uniform throughout the body's lipid content. The body's 2378-TCDD elimination rates are also assumed to be constant throughout the year.

Elimination rate

The first-order elimination rate, $k(t)$, is based on the function developed by Michalek *et al* (1996, as reported by Lorber 2002). The elimination function varies in accordance with the percentage body fat of an individual. Consequently, the values of $k(t)$ change in accordance with the age of the 'individual' modelled.

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The expression used to calculate k(t) is:

$$k(t) = k_o + k_1(F(t) - 25)$$

where k_o is the elimination rate (year^{-1}) for a person with 25% body fat; k_1 is a constant reflecting the change in elimination rate with body fat (year^{-1}); and $F(t)$ is the percentage body fat at year 't' in an individual's life. The model uses the values $k_o = 0.0665$ and $k_1 = -0.00314$ (as reported by Michalek *et al*, 1996) to predict a 2378-TCDD half-life of 10.4 years for a person with 25% body fat.

Pinsky and Lorber (1998) used the same elimination rate formula but derived the values of $k_o = 0.0775$ and $k_1 = -0.00313$. Using these constants, a lower half-life of 8.9 years is calculated for a person with 25% body fat.

Mickalek *et al* and Pinsky and Lorber's estimates were both tested for 'goodness of fit' when calibrating the New Zealand model against the MfE blood serum sampling programme. The higher half-lives calculated using Michalek *et al's* constants best fit the 2378-TCDD concentrations observed in blood lipid samples and were therefore used in the final model. Estimated 2378-TCDD half-lives for females and males of different ages are presented in Figure 2.

Figure 2: Estimated 2378-TCDD half-lives for women and men
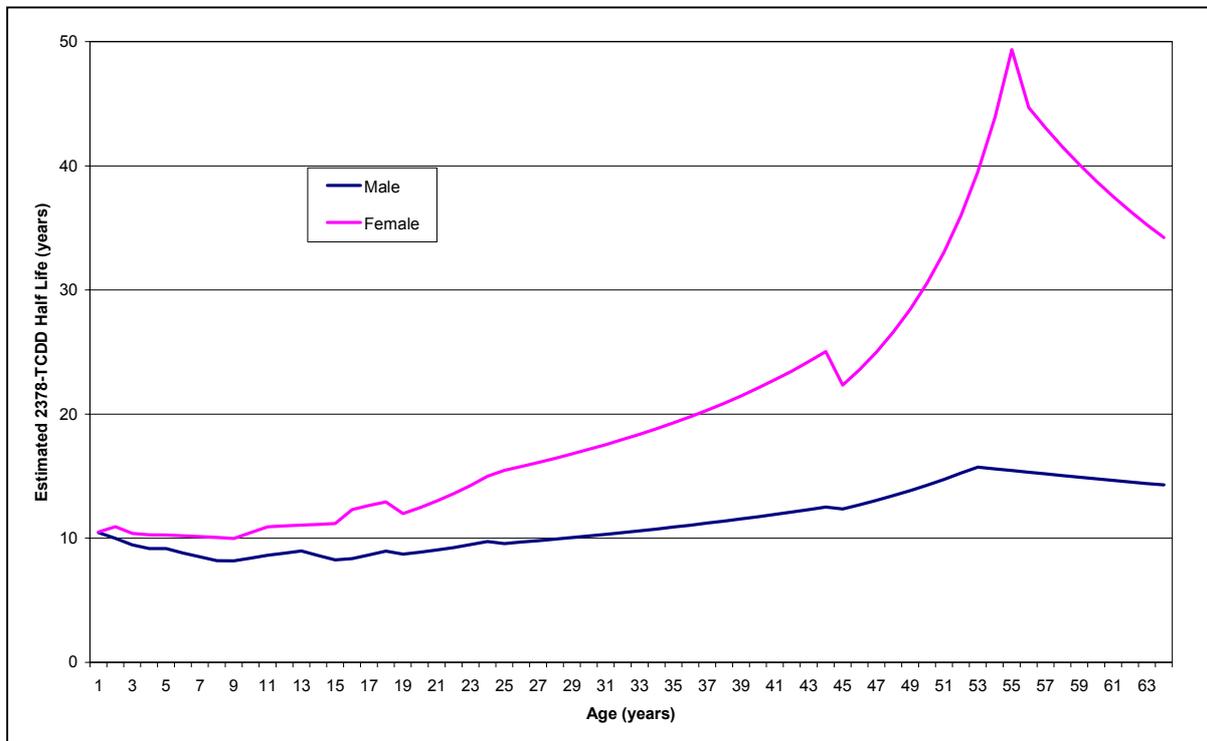
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Figure 2 suggests that the estimated half-lives are generally reasonable for men. For women, however, half-life predictions vary greatly for individuals aged between 25 and 49 years, with extremely high half-lives predicted for women older than 47 years. These elimination rates are at the extreme of rates reported in the literature (MfE, 2001b). It is therefore possible that these upper values do not reflect true population values. This may be because, although Michalek *et al's* values provided the best fit to the observed blood serum concentrations, elimination rates are calculated using percentage body fat profiles compiled from a number of sources using a variety of techniques. Percentage body fat profiles were not derived directly from measurements taken from the New Zealand population.

There may also be a greater level of uncertainty about estimated body fat in women compared to men. It is possible that body fat percentages were underestimated. Thus, Michalek *et al's* higher half-life predictions may be correcting for this underestimation. For women, the elimination rates predicted using Pinsky and Lorber's (1998) constants may actually provide the most accurate reflection. An alternative explanation is that 2378-TCDD intake rates have been underestimated in the model previously, particularly for women.

Whatever the case, the higher than expected half-lives predicted for New Zealand women suggest that special care should be taken when interpreting the results from the female 2378-TCDD toxicokinetic model.

Intake rates

Annual intake rates were calculated using the following expression:

$$I_{TCDD}(t) = D(t).B(t)*365 + X(t)$$

where $I_{TCDD}(t)$ is the annual intake of 2378-TCDD during the year (pg/year); $D(t)$ is the typical daily dietary intake rate (MJ/day); $B(t)$ is the 'background intake' function (pg/MJ); and $X(t)$ is any 2378-TCDD intake defined by the user in addition to background intakes.

Separate dietary intake profiles ($D(t)$) and background intake ($B(t)$) functions were defined for the female and male models. Additional (non-background) intakes, $X(t)$, resulting from a particular industrial exposure can be defined in the Excel Spreadsheet in terms of increased exposure from dietary intake, increased exposure relative to body weight or as a uniform increase in dioxin intakes regardless of an individual's age-dependent dietary intake or body parameters. Additional exposures may be defined for a particular year or range of years.

Energy intake profiles

A number of different sources were used to estimate typical New Zealand lifetime dietary energy intakes. Data for people aged 15 to 64 years was obtained from the *National Nutrition Survey* (MoH, 1999). The *National Nutritional Survey* defines average male and female energy intakes for 5 age groups based on responses from a dietary survey (15-18 year olds; 19-24 year olds; 25-44 year olds; 45-64 year olds, and over 64 year olds).

For children aged up to 7 years, average energy intake profiles were assumed equivalent to the *Ministry of Health* (1997) average Recommended Dietary Intakes (RDIs). For healthy children, these are 5.5 MJ per day for 0 to 3 year olds and 7.0 MJ per day for 4 to 7 year olds. The same intake estimates were used for male and female children. For children aged between 8 to 11 and 12 to 14 years, average energy intakes were derived from the New Zealand RDIs for adolescents (MoH, 1998). Table 1 lists the energy intake estimates used in the model.

Table 1: Estimated daily energy intakes for different age groups (kJ/day)

Age Group	Female	Male
1-3 years	5500	5500
4-7 years	7000	7000
8-11 years	7950	8900
12-14 years	8775	10500
15-18 years	8862	12430
19-24 years	9102	13247
25-44 years	8417	12904
45-64 years	7386	11134
65 years and over	6579	9274

To ensure a smooth transition in energy intake rates between each year of an individual's lifespan, linear interpolation functions were used. These functions smoothed transitions between different age groups while maintaining each group's average energy intake rate. The predicted energy intake profiles are presented in Figure 3. It is assumed that age-dependent dietary energy intakes have remained relatively constant between 1937 and 2000.

Figure 3: Predicted energy intake profiles

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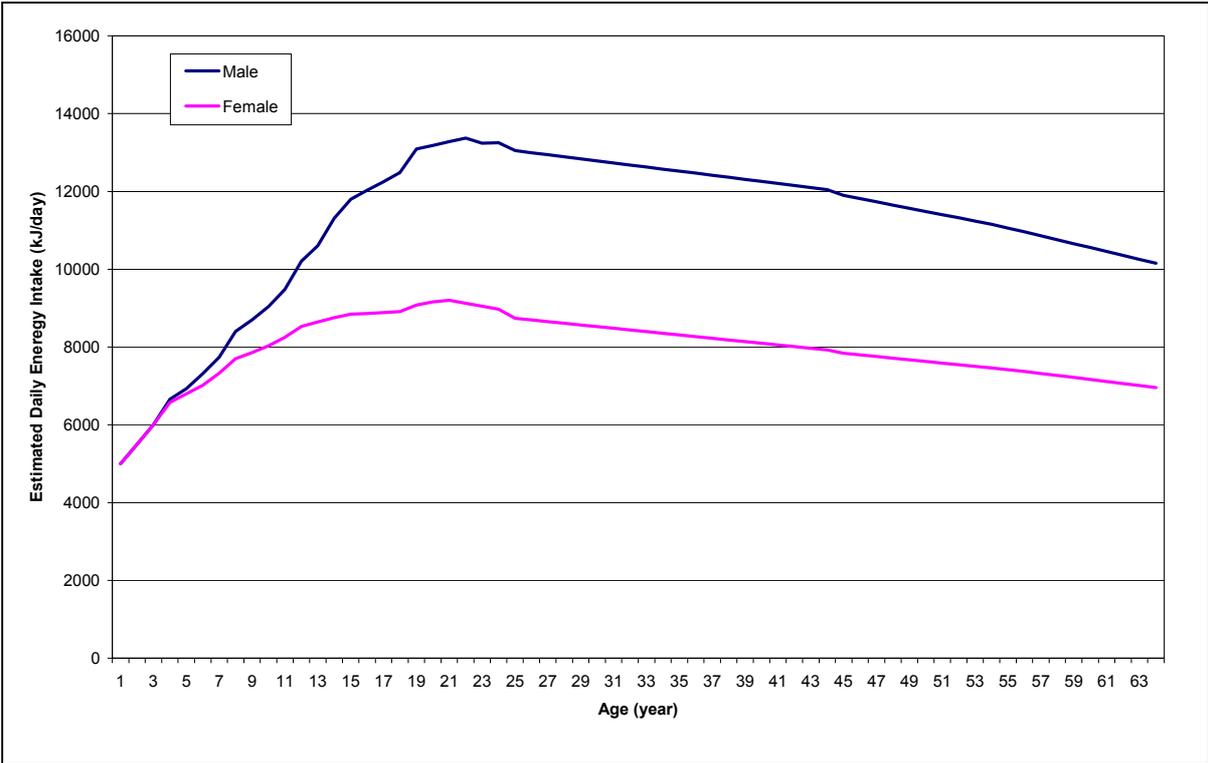
Background intake function

The background intake function, B(t), corrects for the amount of 2378-TCDD ingested per megajoule of food consumed by an individual. The amount of 2378-TCDD in food varies in different time periods according to rates of dioxins emitted into the environment and accumulated in the food chain. Present day dioxin concentrations in food have reduced since the 1950s and 1960s due to increased awareness of the impact of dioxins and changes in industrial processes, products and emission controls.

The model uses a 'background function' to simulate changes in 2378-TCDD food concentration between the years 1937 and 2000. The function is derived from a 'correction function' developed by Van Der Molen *et al* (1996). Van Der Molen *et al* used the function to account for historical changes in food contaminant concentrations and changes in eating habits. The authors fitted a function to observed TCDD concentrations in blood lipids in the Dutch population assuming constant, but different, elimination rates for males and females. The 'correction function' is:

$$B(t) = A + H.C ((G - t + 1922) / B)^{C-1} \exp(-(G - t + 1922) / B)^C)$$

where A, B, C, G and H are constants used to fit the function to the observed data. Parameters A and H alter the function's height. Parameter B scales the function over the time axis. Parameter G shifts the function over time and parameter C determines the shape of the function (Van Der Molen *et al* 1996).

The function was optimised with parameters A = 0.1, B = 60, C = 3.5, G = 95 and H = 1.3471. Peak food TCDD concentrations were predicted to occur in 1962. The 'correction function' used in Van Der Molen *et al's* toxicokinetic model is:

$$B(t) = 0.1 + 4.715.((2017 - t) / 60)^{2.5} \exp(-(2017 - t) / 60)^{3.5})$$

The New Zealand toxicokinetic model's 'background intake' function uses the same parameters as Van Der Molen *et al*. The values of parameters B, C and G, used to alter the shape and timescale, were assumed equal to those derived by Van Der Molen *et al*. Only parameters A and H, altering the function's height, were optimised for New Zealand conditions and 2378-TCDD blood lipid concentration data.

Van Der Molen *et al's* (2000) revised dioxin and furan toxicokinetic model used the same correction function to estimate potential exposures in the Dutch population, but readjusted the A and H parameters to better fit historical measurements of dioxin concentrations observed in food. In this model, the correction function was used only to simulate background exposures prior to 1978. Dioxin intake levels for years after 1978 were based upon dioxin concentration levels recorded in food samples taken in the years 1978, 1984/85 and 1994. Years in between these times were estimated with a linear interpolation function. Since historical food contamination data was not available in the New Zealand context, this approach was not used in the New Zealand 2378-TCDD exposure model.

Optimising the background function

In the New Zealand model the optimised background intake function was:

$$B(t) = \mathbf{J}x0.1 + \mathbf{K}x4.715.((2017 - t) / 60)^{2.5} \exp(-(2017 - t) / 60)^{3.5})$$

where the parameters J and K were such that the 2378-TCDD blood lipid concentrations (ng TEQ/kg lipid) predicted for the year 2000 were as close as possible to the 2378-TCDD blood concentrations recorded during the MfE organochlorides blood serum sampling programme. Different values of J and K were optimised for the female and male models. In other words, different background functions were developed for each gender.

Male and female 2378-TCDD blood lipid concentrations were derived for four of the five age groupings used in the MfE organochlorides blood serum sampling programme (15-24 year olds; 25-34 year olds; 35-49 year olds, and 50-64 year olds). Table 2 summarises the MfE 2378-TCDD blood lipid concentrations.

The fifth MfE age grouping (65 years and older) was not used in the optimisation procedure or simulated in the model. This is because the upper age of people in this group was unknown, making it difficult to simulate the group's average 2378-TCDD blood lipid concentration. Also, relative to the other age groups, there was a high degree of variability in the samples of 2378-TCDD blood lipid concentrations for those aged 65 and older. Therefore, it was difficult to define an average 2378-TCDD concentration for this age group.

Table 2: 2378-TCDD blood lipid concentrations (ng TEQ/kg lipid) derived from the MfE organochlorides blood serum sampling programme

Age Group	Female	Male
15-24 year olds	1.1	1.0
25-34 year olds	1.6	1.3
35-49 year olds	2.2	1.8
50-64 year olds	3.6	2.5

The parameters J and K were optimised using a specially written JAVA software program. The program incorporated all of the algorithms and assumptions in the Excel Spreadsheet model, although no provision was made for non-background exposures. The program assessed the difference between predicted and observed 2378-TCDD concentrations using different values of J and K. The function was assumed to be optimised for the values of J and K when this difference was smallest. The parameters J and K were optimised using incremental steps of 0.1.

The difference was calculated using the function:

$$\text{Diff}^2 = (\text{Obs}_{15\text{-}24} - \text{Pred}_{15\text{-}24})^2 + (\text{Obs}_{25\text{-}34} - \text{Pred}_{25\text{-}34})^2 + (\text{Obs}_{35\text{-}49} - \text{Pred}_{35\text{-}49})^2 + (\text{Obs}_{50\text{-}64} - \text{Pred}_{50\text{-}64})^2$$

where 'Obs' refers to the MfE's observed age group blood lipid concentration and 'Pred' refers to the predicted age group blood lipid concentration. Predicted age group concentrations were calculated using the average of each 'individual' 2378-TCDD blood lipid concentration predicted for the age grouping in the year 2000. There was no weighting to account for the varying range of ages included in each group.

This optimisation analysis assumes that the average 2378-TCDD blood lipid concentrations derived from the MfE organochlorine blood serum sampling programme are generally representative for the age groups included. Unfortunately, there is no indication in MfE documentation about the age distribution of the blood samples taken from participants in the study. The optimisation analysis could be refined if this data were available in future.

Table 3 lists observed 2378-TCDD blood lipid concentrations and those predicted by the model. The table also lists the range of 2378-TCDD blood lipid concentrations predicted for the individual ages in each age group, from which the average was derived. Generally the maximum and minimum predicted 2378-TCDD blood lipid concentrations were similar to both the average measured and predicted concentrations, particularly for the younger age groups and males. This suggests that optimising the model and predicted background 2378-TCDD intake rates would not be influenced greatly if the MfE blood serum samples were taken from an unrepresentative age distribution. There is a relatively high degree of variation in predicted 2378-TCDD blood lipid concentrations for women over 35 years, however. In this instance, 2378-TCDD blood lipid concentrations derived from an unrepresentative sample could affect the optimised model parameters more significantly.

Table 3: 2378-TCDD blood lipid concentrations (ng TEQ/kg lipid) recorded by the MfE and predicted by the optimised pharmacokinetic model

Age Group	Female population			Male population		
	MfE	Model		MfE	Model	
	Average	Average	Range	Average	Average	Range
15-24 year olds	1.1	1.0	(0.8, 1.2)	1.0	0.9	(0.7, 1.1)
25-34 year olds	1.6	1.6	(1.3, 1.9)	1.3	1.4	(1.2, 1.6)
35-49 year olds	2.2	2.5	(2.0, 2.9)	1.8	1.9	(1.7, 2.1)
50-64 year olds	3.6	3.4	(2.9, 4.2)	2.5	2.4	(2.1, 2.8)

Although the model provides a reasonable fit of predicted to observed 2378-TCDD blood lipid levels, further work would likely improve the 'fit' by adjusting parameters influencing the shape, timescale and maximum food concentrations. In the current model, these parameters are assumed to be consistent with Van Der Molen *et al's* (1996) correction function. Therefore, in its present form, the background function is intended to provide only an initial estimate of likely historical 2378-TCDD exposure rates.

Some preliminarily examinations were undertaken to assess the effect of altering the predicted year of peak 2378-TCDD concentrations. These preliminary investigations suggest that a better fit would be obtained if peak exposure occurred in a year earlier than that currently used (1962). These results were not used in this initial assessment due to uncertainties in the age-dependent body profile and elimination rate parameters.

Figure 4 illustrates the predicted historical background intake function calculated using the optimised parameters. The function shows the predicted typical intakes for a male and female with a dietary energy intake of 10.8MJ per day.

Figure 4: Predicted 2378-TCDD background intake function for 10.8MJ/day diet (pg TEQ/day)
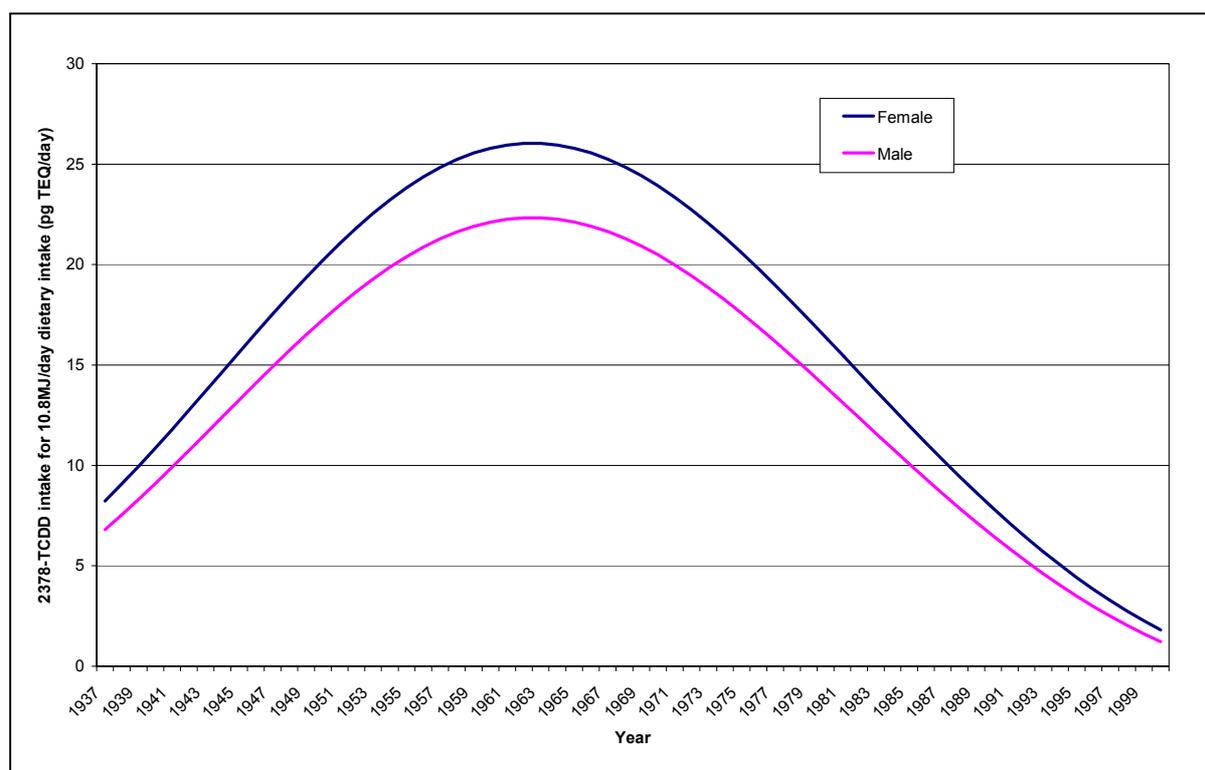
The estimates for males and for females in Figure 4 are obtained from separately-optimised versions of the model that allowed the 2378-TCDD content of the food to vary independently for males and females to give the best match with the MfE blood lipid levels. Because of the marked differences in body composition and therefore dioxin half lives between males and females, the relatively close agreement (within about 20%) in these two were largely independent estimates of the 2378-TCDD content of food over time, expressed on a per megajoule basis, indicates that the model is fairly robust, assuming that the model input parameters used in the (most notably percentage body fat and 2378-TCDD elimination rates) are an accurate representation of the actual population and toxicokinetic properties.

It should also be noted that the background intake function was calibrated against 2378-TCDD blood lipid concentrations from people where no specific dietary intake information was available. The calibration also assumes that dietary energy intakes in 1997 were the same as those in prior years.

Age-dependent parameter profiling

Age-dependent parameter profiles for total body weight; lipid percentage of total body weight; daily energy intake, and half-life were compiled for a 'typical' New Zealand female and male. The methodology used to develop the dietary energy intakes and half-life profiles has been discussed previously. The techniques used to estimate body weights and body fat are outlined below.

Body weight

Body weights were calculated using national and international data. For children aged between 1 and 5 years, body weight data were obtained from the *Ministry of Health*. For children aged between 6 and 14, average body weights were sourced from the *US EPA* exposure factors handbook. Body weights for people aged between 15 and 64 were estimated using averages recorded for 4 age groupings in the *National Nutrition Survey* (1997; 15-18 years, 19-24 years; 25-44 years; 45-64 years). To ensure relatively smooth transitions between age groupings, linear interpolation functions were used to estimate year-by-year changes in body weight. The functions were defined such that the average body weight of each age group was maintained.

Percentage lipid

The total percentage of body weight present as lipid was estimated by calculating the lipid concentration in the blood, bone, liver, fat, muscle and remaining organs. Van Der Molen *et al* (1996) describe a method for calculating total weight and percentage weight of lipids for each of these body components using age-dependent functions. Different parameter values were defined for males and females. These functions were fitted to population data derived primary from the Netherlands. These functions cannot be directly applied to a New Zealand population without accounting for differences in the average weight and body fat (adipose tissue) of individuals on a year-by-year basis.

According to Van Der Molen *et al's* (1996) description, the proportion of total body weight associated with blood, bone, liver and other remaining organs remains constant on a year-by-year basis. Therefore, the weight of each of these organs in a typical New Zealander, and consequently weight of lipid, can be calculated for each year of an individual's life by multiplying the estimated weight of the New Zealand 'individual' by the percentage of total body weight associated with each organ (calculated using Van Der Molen *et al's* model for the same year).

$$\text{NZ Organ Weight (t)} = \text{NZ Total Body Weight (t)} \times \frac{\text{Netherlands Organ Weight (t)}}{\text{Netherlands Total Body Weight (t)}}$$

Van Der Molen *et al* used the following function to calculate total body, blood, liver, bone and other body organ weights (in kg):

$$\text{Netherlands Organ Weight (t)} = A.t + B(1 + C.EXP(-D(t - E)))^{-1/C}$$

where A, B, C, D and E are constants and 't' is the age of the individual (defined in years). The values of the constants are gender dependent. The lipid weight associated with each organ is estimated by multiplying the total organ weight by the percentage lipid content associated with each individual body component. A summary of the parameter values used in the model is presented in Table 4.

Table 4: Van Der Molen *et al's* (1996) body weight model parameter values

Gender	Parameter	Body Weight	Blood Weight	Bone Weight	Liver Weight	Remaining Organs
Male	A	0.0307	0	0	-0.008	0
	B	76.2	6.2971	10.7315	1.926	7.8182
	C	3.922	3.922	3.922	1.926	3.922
	D	0.4641	0.3176	0.5239	0.2273	0.3678
	E	13.488	11	12	8.666	8.4081
Female	A	0.1959	0	0	-0.00695	0
	B	57.497	4.99	8.7319	1.758	6.095
	C	4.617	4.617	4.617	4.617	4.617
	D	0.572	0.455	0.8588	0.3309	0.39366
	E	11.333	8	8	12.478	6.5582
Both	% Lipid	-	0.0052	0.186	0.049	0.049

The percentage of total body weight consisting of adipose tissue was calculated using a number of different sources, based on the availability of reliable data from which to estimate typical New Zealand values.

For individuals aged 2-5 years and over 16 years, numerical expressions developed by Deurenberg *et al* (1991) were used to estimate average body fat content. Deurenberg *et al's* formula was derived using body mass index (BMI), age and gender parameters to predict average percentage body fat based on measurements taken from the Dutch population. Different formulas are used to estimate the body fat of children (1-15 year olds) and adults (over 15 years):

Children % Adipose Tissue = 1.51 x BMI-0.70 x age - 3.6 x sex + 1.4

Adult % Adipose Tissue = 1.20 x BMI + 0.23 x age - 10.8 x sex - 5.4

where BMI is the body mass index; 'age' is inserted in years, and 'sex' is a gender dependent parameter (sex=1 for male and sex=0 for females). An average population body mass index (BMI) is calculated as the total body weight (kg) divided by the square of the individual's height (m).

Both Pinsky and Lorber (1998) and Lorber (2002) used Deurenberg *et al's* method to estimate typical American body profiles for their respective toxicokinetic models.

In the New Zealand model, Deurenberg *et al's* method was applied only to the 2-5 year age group and those aged 16 and above. This is because height and weight measurements, necessary for calculating the average BMI, were available only for these groups.

For those aged 2 to 5 years, height data was compiled from the *Ministry of Health* (1997). Heights for females and males aged over 15 years old were taken from the *National Nutrition Survey* (1999). Average heights were defined for four age groups (15-18 year olds, 19-24 year olds; 25-44 year olds; 44-64 year olds). Due to the relatively small height differences between age groups, no interpolation function was needed to smooth the age-dependent height profile for people aged over 18 years. To account for growth between the ages of 15 and 18, it was assumed that New Zealand children grow at a year-by-year rate proportional to American adolescents (as reported by the USEPA, 2000), although the average height reported for New Zealanders in the 15 to 18 year group was maintained (MoH, 1999). The approach used to estimate total body weight is described above.

The formulas used may not account for New Zealand's unique ethnic composition, lifestyle and diet. Consequently, the percentage adipose tissue profiles should be considered an approximate estimate of population trends. Also, the model body profiles do not take into account changes in average body fat composition between 1937 and 2000.

Other age related percentage adipose tissue values (for children 1 year old and children aged 6 to 14 years) were estimated from discreet gender-specific values reported by Guo (1998) and the *National Research Council* (1993). Other values were interpolated from surrounding values.

It was assumed that 85.9% of the total adipose weight was lipid (Van Der Molen *et al*, 1996). Therefore, total adipose lipid weight was calculated by multiplying the percentage of total body weight estimated to be adipose tissue by the total body weight times 85.9%.

Total muscle weight was calculated as the residual body weight once the weight all of the other body components were subtracted from the total body weight. In accordance with Van Der Molen *et al* (1996), it was assumed that 6.4% of the muscle weight was lipid.

The predicted total weight of each body component with respect to age is presented in Figure 5. Males have a higher proportion of predicted muscle weight to adipose tissue compared with females.

Figure 6 presents the relative contribution of each body component to the body's total lipid content and the percentage of total body weight predicted to be lipid. The model suggests that adipose tissue is the single largest source of lipid in the body. Figure 6 also highlights the higher percentage of body weight predicted to be lipid in females relative to males.

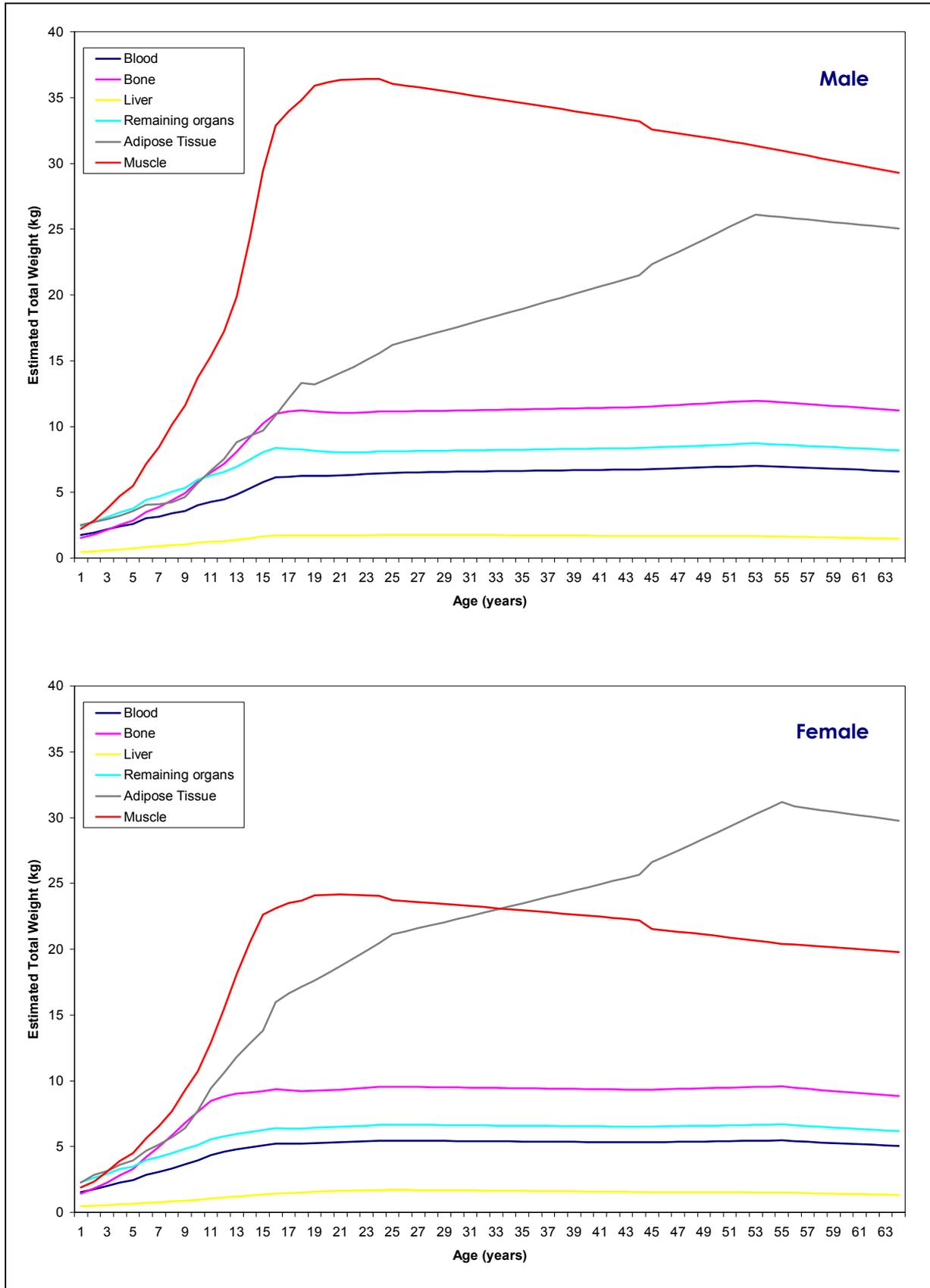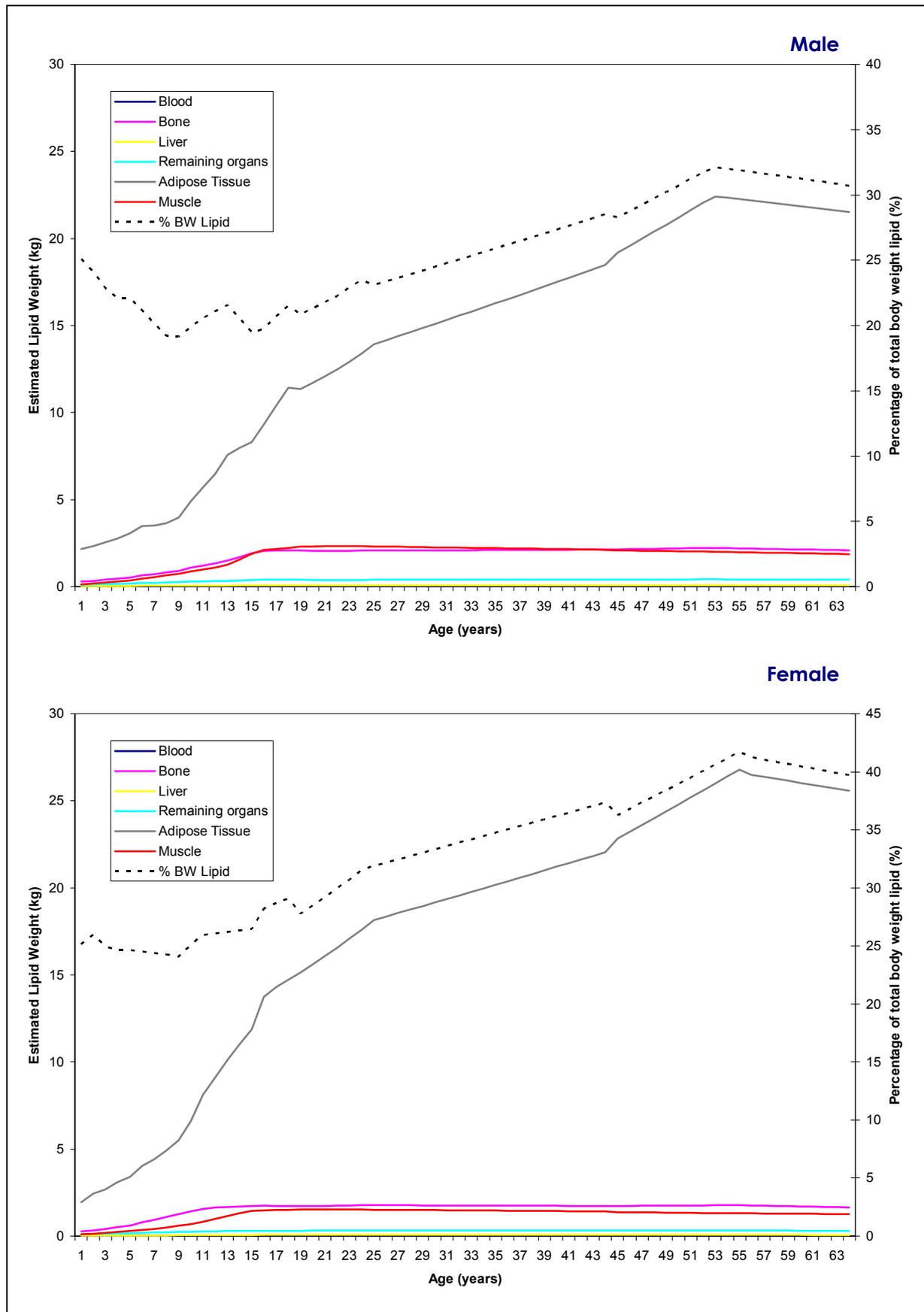**Figure 5: Predicted body component weights for males and females**

Figure 6: Predicted lipid weights associated with each body component and total percentage of body weight lipid for males and females

Uncertainties

The toxicokinetic model is based upon a number of assumptions. Each assumption contains a degree of uncertainty that will affect the accuracy of predicted 2378-TCDD blood lipid concentrations. The model is in an initial developmental state and its findings should therefore be treated with extreme care. It is intended to provide an initial estimate of background exposures in New Zealand based upon derived contaminant intake rates and life history body profiles. Further work is needed to review and refine the assumptions upon which the model is based. This section highlights a number of issues that need further consideration.

Body profiling and half life estimates

A number of different age-dependent body parameters were incorporated in the model. Many of these parameters have been modelled using a variety of information sources. The quality of the data and estimation techniques used will directly affect predicted 2378-TCDD concentrations.

Body parameter profiles developed from international sources may not accurately reflect New Zealand's unique lifestyle and ethnic composition. For instance, age-dependent body fat profiles were estimated largely using relationships developed by Deurenberg *et al* (1991) from Dutch population data. These relationships may not provide an accurate reflection of New Zealand trends. As body fat determines the elimination rate of 2378-TCDD and the dilution of 2378-TCDD accumulated in body fat, this may be one of the more critical uncertainties in the model requiring further review.

These uncertainties may have the most significant impact in the female toxicokinetic model. In this model, low 2378-TCDD elimination rates in the body are predicted using Michalek *et al's* (1996) formula. The estimated elimination rates of 2378-TCDD are much lower than those reported in the literature. However, actual 2378-TCDD elimination rates in older women do not appear to be well documented. This suggests that the model may or may not accurately simulate historical 2378-TCDD intake and accumulation rates. Faster elimination rates would require significantly higher historical background intake rates to offset the increased decline of 2378-TCDD in the body over time.

Faster 2378-TCDD elimination rates, more typical of values identified in the literature, would be predicted if lower percentage body fat values were estimated for New Zealand females. But it is important to note that a lower percentage body fat value would also mean a lower dilution of accumulated 2378-TCDD in the body. Consequently, the concentration of 2378-TCDD per kilogram of lipid would increase. In other words, changing this parameter does not necessarily produce a predictable linear outcome.

Although no sensitivity analysis was conducted, it is possible that lower dilution of accumulated 2378-TCDD in the body lipid content may partly compensate for the lower than expected elimination rates predicted for females. Therefore, the model may predict reasonable values for 2378-TCDD intake rates, although the mechanics of the model may not simulate the dilution and elimination of the contaminant accurately.

An alternative explanation is that Michalek *et al's* formula overestimates the effect of body fat on elimination rates. The slower 2378-TCDD elimination rate function derived by Pinsky and Lorber (1998) may provide more realistic estimates of intake rates.

Due to these uncertainties in the female model, special care is needed when using predicted values to estimate actual exposures. Although uncertainties associated with the male model appear to be less pronounced, further work is required to refine assumptions about body fat and 2378-TCDD elimination rates in both the female and male model.

The model does not make any attempt to examine changes in the composition of the New Zealand population between the years 1937 and 2000. Over this period, population dietary habits, energy intake rates and body parameter trends would likely vary due to changes in lifestyle, ethnic composition, health of the population and the availability of different foods. Ideally, it would desirable to include these time-dependent effects in the model. Limitations associated with data collection and profiling may reduce any potential benefits from this more detailed approach, however.

Changing intakes rates of 2378-TCDD due to the concentration of dioxins in food and broad changes in dietary habits were both simulated by the background intake function to some extent. It is possible that we may obtain a better 'fit' to observed 2378-TCDD blood lipid concentration levels by allowing the background intake function to vary in wider degrees of freedom (only two of the five background function variables have been optimised in the model). This further analysis would only reduce uncertainty in the model if all of the other assumptions are simultaneously reviewed - otherwise the recalibrated function may only provide a better 'fit' to a potentially flawed data set.

The 2378-TCDD intake rates modelled by the background intake function were based on an individual's typical daily energy intake. The calculation procedure assumed that the concentration of 2378-TCDD per megajoule of food consumed is constant in any particular year. The model does not account for changes in an individual's dietary composition over the lifespan and hence changes in the amount of 2378-TCDD per megajoule of food consumed. For instance, if the proportion of an individual's dietary energy intake associated with food with high concentrations of 2378-TCDD changes significantly over their lifetime, then the current calculation procedure may not accurately estimate 2378-TCDD intakes.

The situation is further complicated if changes in food preferences between 1937 and 2000 are considered. The relative intake of 2378-TCDD per megajoule of energy consumed may vary between age groups and also over the years modelled.

The model estimates 2378-TCDD intakes of a 'typical' female and male using average food intake and body parameter profiles based upon available statistic information. Thus, the model assumes that the lifecycle of a 'typical' individual can be represented by derived population averages. The model also assumes that the sample of individuals included in the MfE blood serum sample (and used to optimise the background intake function) are representative of a 'typical' New Zealand population and consequently the derived input 'individual' parameter profiles.

Alcock *et al* (2000) suggest that body parameters such as the percentage body fat and body weight, which are critical to predicting accumulation and concentration of 2378-TCDD in the body, may vary significantly in a population. The sensitivity of the model has not been assessed regarding potential deviation from assumed 'typical' population parameter values or the representativeness of the MfE sample of participants. Further work in this area could be useful to define the limits of predicted background intake rates by reviewing the validity of chosen input parameters or by assuming variation in the predicted body profiles that may reflect possible deviations from predicted norms.

Mother-child interactions

The model assumes that there is no direct interaction between mothers and children regarding the intake and transfer of 2378-TCDD. The model assumes that a child is born with a zero 2378-TCDD body burden and that the intake rate of contaminants corresponds solely to the amount of food ingested and the historical concentration of 2378-TCDD in the food at the time of ingestion. There are three main interactions between mother and child that the model does not consider:

- Accumulation of 2378-TCDD in the unborn child.
- Intake of 2378-TCDD in the child from breastfeeding.
- Loss of 2378-TCDD body burden in the mother from breastfeeding.

2378-TCDD intake rates in neonates and unborn children are linked to the level of 2378-TCDD in the mother. Modelling both of these intake rates requires an understanding of the historical intake and elimination rates in the mother and the degree of contaminant transfer from the mother to the child. Deriving values of 'typical' breastfeeding behaviour is potentially problematic. Breastfeeding trends are likely to vary considerably throughout the New Zealand population according to ethnicity, location and time. Developing a reliable longitudinal model that describes this behaviour may not be practical. Also, as the MfE blood serum study does not appear to have collected information about previous or current breastfeeding behaviour, it may difficult to accurately calibrate the model using pooled 2378-TCDD blood lipid concentrations with such a breastfeeding behavioural profile.

There are also uncertainties associated with estimating the transfer of 2378-TCDD between a mother and unborn child. To account for the impact of either transfer or breastfeeding, the model would need to be reconfigured to estimate the mother's historical body burden (from which a suitable child intake could be estimated).

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In their toxicokinetic model for PCBs, Alcock *et al* (2000) suggest that after the age of 10 years the effect of breastfeeding on an individual's overall PCB body burden is minimal. Alcock et al's model assumed a reference half-life of PCBs in the body of 10 years for a 40 year old. In the New Zealand toxicokinetic model, a comparable 2378-TCDD half-life of 11.7 years was estimated for males. This suggests that the effect of breastfeeding on 2378-TCDD body burden may also be minimised by adolescence. Although significantly higher 2378-TCDD half-lives are estimated for older women, half-lives are comparable to males' for females under the age of two. Consequently, both the male and female models would likely behave similarly if additional 2378-TCDD intakes (transfer and breastfeeding) were incorporated. Including 2378-TCDD intakes associated with breastfeeding would not be likely to significantly improve the accuracy of the model.

Alcock *et al* (2000) did suggest that breastfeeding may significantly reduce the body burden of PCBs females, however. As noted above, it would be difficult to fully simulate breastfeeding behaviour in the population. This would also require some reformulation of the model to explicitly simulate increased elimination rates of 2378-TCDD. Currently, such effects are only accounted for by the background intake function. The background intake function is optimised to best simulate typical population 2378-TCDD body burden by adjusting the estimated 2378-TCDD intake rates rather than accounting for increased elimination rates.

If the findings of the model are to used to compare typical historical exposures of 2378-TCDD against women who may have been exposed to elevated levels of 2378-TCDD, it would be important to understand assumptions about breastfeeding behaviour that have implicitly been incorporated into the model of a 'typical' New Zealand female. Ideally, it would be preferable if a historic profile of breastfeeding behaviour in New Zealand could be constructed, but this is likely to be difficult to achieve.

Summary and recommendations

The New Zealand toxicokinetic model is a dynamic model capable of predicting the average historic intake rates of 2378-TCDD and average 2378-TCDD concentration in body lipid for women and men between 1937 and 2000. The model uses a linear first order differential equation to estimate total 2378-TCDD body burdens on a year by year basis.

The model uses profiles of food intake rates, 2378-TCDD elimination rates, total body weight and percentage total body fat to estimate the accumulation of 2378-TCDD in people aged between 15 and 64 years (in the year 2000). Each of the profiles is intended to represent changes in body growth and dietary habits over the lifetime of typical female and male New Zealanders. These profiles have been constructed from a wide variety of sources.

The 2378-TCDD intake was based on assumed average concentrations of 2378-TCDD in food consumed between 1937 and 2000. Different parameters in the background intake function were calibrated using the results from the MfE blood serum study which measured the concentration of 2378-TCDD in the blood lipid content of over 1800 volunteers.

Although the model has a high level of agreement with observed 2378-TCDD blood lipid concentrations, there are a number of uncertainties. Most notably are estimations of body fat and associated 2378-TCDD elimination rates in females. There is also a degree of uncertainty associated with modelling 2378-TCDD loss in breastfeeding mothers. Findings from the model should therefore be treated only as broad initial estimates of background intake rates in New Zealand.

But the uncertainties of the model need to be placed in the context of the model's function. The primary purpose of the model was to provide assistance in the selection of individuals to be included in the blood serum sampling programme that may have been exposed to elevated levels of 2378-TCDD. The model aimed to provide insight as to whether current 2378-TCDD blood lipid concentrations are likely to show evidence of an individual exposure to elevated levels in the past (i.e. 1960s and 70s) and what the magnitude of these additional intakes are likely to have been in comparison to average population exposures.

Based upon derived dietary trend rates, elimination rates and body profiles, typical background intake rates have been estimated. Similarly the likely influence of past exposures to elevated 2378-TCDD levels can also be evaluated with respect to the calculated 'average' New Zealand population exposures.

The model is calibrated using population average 2378-TCDD blood lipid concentrations derived from the MfE sampling progamme. However, estimates of standard deviation of the pooled 2378-TCDD concentrations indicate that individual blood serum concentrations can vary considerably, probably by factors in the range 2-4. Consequently individual exposure and/or accumulation rates of 2378-TCDD are likely to vary considerably, possibly more so than the uncertainties inherent in the model. The MfE sampling results suggest that 2378-TCDD exposure and accumulation rates need to be considered on an individual basis.

The agreement between the male and female estimates of 2378 TCDD per mega-joule of dietary intakes suggests that the model might be robust enough for such an analysis if input parameters could be sufficiently defined to take into account an individual's life history. However, an initial assessment of the intake function variability would be required

Recommendations for further development

The following recommendations are made regarding further development of the model:

- There is a need to review the representativeness of female and male body profiles. Of particular importance is the characterisation of female percentage body fat profiles.

- There is a need to review the elimination rates predicted using Michalek et al's function, particularly regarding elimination rates predicted for older females.

- There is a need to review the representativeness of participants in the the MfE blood serum study.

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- It may be worthwhile to assess the potential effect of breastfeeding on 2378-TCDD accumulation and elimination rates in mothers. The model could be developed to allow quantification of the effects of different breastfeeding behaviour on 2378-TCDD blood lipid concentration. This type of assessment will be important if results from the model are to used as a point of comparison of 2378-TCDD blood concentrations taken from individuals exposed to higher than normal contaminant levels.

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