BODY BURDEN VARIABILITY AND SAMPLE SIZE ESTIMATION

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Introduction

The 1999 Belgian dioxin-incident led to great concern about serious health effects in the general population. Since then, no major adverse health effects which could be linked to the accident have been observed. This is, however, not unexpected because of the large variation in exposure rates in the overall Belgian population and the limitations of epidemiological surveys to detect slight increases in particular pathological conditions. The contamination by polychlorinated dibenzo-p-dioxins (PCDD), dibenzofurans (PCDF) and biphenyls (PCBs) was, however, important enough—at least in part of the food chain—to have an impact on the daily intake of the population directly exposed to theseontaminated food items, and hence on their body burden (BB). A study is, therefore, planned to assess the body burden in a sample of thehighly exposed population and to compare it with the body burden in a control population. It is more especially of interest to know whether, within the potentially exposed population, the body burden reached levels of about 30 ng TEQ TCDD/kg bw, which are known to be accompanied by detectable adverse effects in the experimental animal. In order to calculate the number of subjects to be included in the study an estimation of BB variability in the general population is required.

Methodological approach

Under steady state conditions the "dioxin" body burden is computed as: $BB = d \times f \times t_{1/2} / ln2$ where BB is the body burden in ng TEQ TCDD/kg bw, d is the daily intake measured in ng/kg bw/day, f is the fraction of the dose absorbed, and $t_{1/2}$ is the dioxin half-life in days.

Assuming that the median background body burden in Belgium is around 4 ng TEQ (PCDD/F) /kg bw, increasing towards 8 to 12 ng TEQ TCDD/kg bw when the intake of "dioxin-like" PCBs is also included (2-3-fold increase)[1], a 2.5 times increase in total "dioxin" body burden would bring it towards 20-30 ng TEQ TCDD/kg bw. This reaches the body burden range where toxic health effects have been observed in controlled animal experiments. It is generally accepted that at similarbody burdens similar risks can be expected in man. Provided this increase really happened in the highly exposed group, the study sample size should be large enough to detect it.

Since the distribution of body burdens is usually right skewed, it is current practice to assume that the natural logarithm of the body burden is normally distributed. Translation of the expected 2.5 increase in body burden into the natural logarithmic scale, means an additive increase of ln (2.5) = 0.92 inln BB. Furthermore, in the ln scale, the variance of the ln BB is the sum of the variances of the ln of the three parameters d, f, and $t_{1/2}$.

In order to assess the variability of the dose *d*, an analysis of variance of the intake of the 2,3,7,8 chlorine substituted PCDDs, PCDFs and non-ortho PCBs was performed using the intake data from 5898 individuals from the Dutch population which were made available to us by Liem and Theelen[2]. While the intake of each individual congener was available separately, we first computed the total TEQ intake value according to the WHO Toxic Equivalent Factors. Figure 1 summarizes the data for the TEQ intake as well as for the logarithm of the TEQ intake. The estimated standard deviation of the ln intake is 0.56.

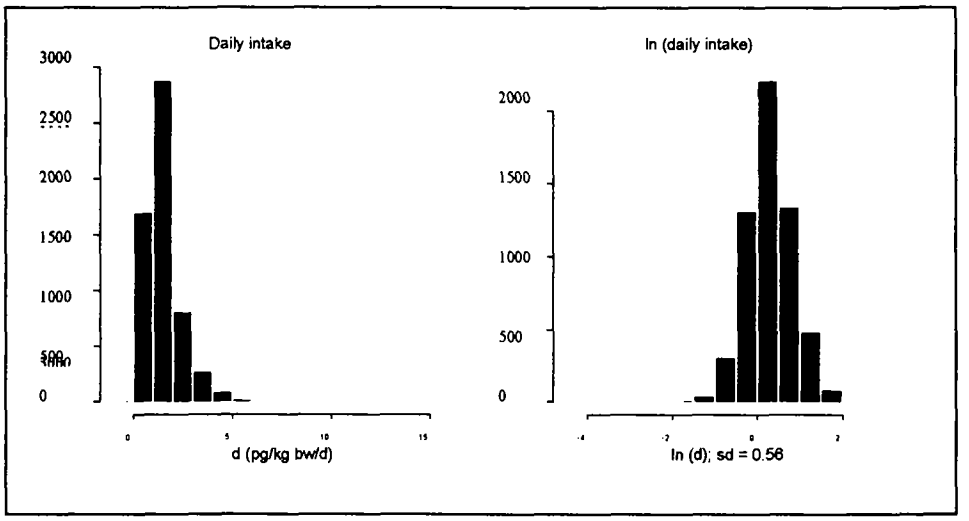

Figure 1: Histogram of daily intake (pg/kg bw/d) and ln daily intake.

Numerous recent studies[3,4,5] have tried to characterize the elimination of dioxin congeners, applying a simple one compartment pharmacokinetic model on concentrations found in multiple biological samples from cohorts of highly exposed subjects. The half-lives reported in those studies differ quite substantially due to differences observed in study design, methodology and modeling. Within the context of our sample size computation, we considered the elimination of the total TEQ amount and we assumed ln normal statistical models for the between-subject variability in d and $t_{1/2}$ as follows:

$$\begin{cases} d_i = d \times e^{\eta_{1,i}} \\ t_{1/2,i} = t_{1/2} \times e^{\eta_{2,i}} \end{cases}$$ where the between patient variabilities, $\eta_{1,i}, \eta_{2,i}$ are multivariate normally

distributed with means 0 and variance, covariance matrix:

$$\begin{pmatrix} 0.36 & 0 \\ 0 & 0.36 \end{pmatrix}$$

In the logarithmic scale, we assumed a similar variability for elimination and intake. The histogram presented in figure 2, shows the distribution range for half-lives according to the above model when a median half-life of 2555 days (7 years) is assumed. Figure 2 shows that the simulated variability in half-life covers the range of half-lives reported in the literature.

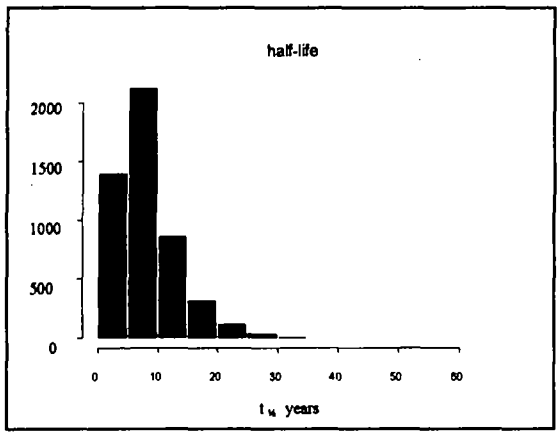

Figure 2: Simulated half-life histogram.

The literature describing the absorption of those compounds is sparse. The studies are usually based on a restricted number of subjects (1 or 2) and no between subject variability can be assessed. Sample size computation is, therefore, proposed for a range of possible variability in ln absorption.

Results and discussion

Assuming that a Student t-test, with a power of 90 %, will be used to compare the ln body burden between the highly exposed subjects and the control group, the requested sample sizes in each group are reported in the following table and this for different possible variabilities in absorption.

sd(ln(f))	0.2	0.4	0.6	0.8	1.0
sample size	20	23	28	35	44

A sample size of 40 independent subjects in the study group as well as 40 subjects in the control group appears to be a reasonable number in order to detect, with a 90% power, a 2.5 increase in body burden. The approach proposed in this paper could be more precise if we could consider the different congeners separately. Since it is difficult to make a reasonable

choice between the published half-lives values, an unified population approach allowing for random intake as well as random elimination in the estimation of half-lives was necessary.

References

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