

Appendix B

Statistical Analysis for Prediction of DINP Intake by Young Children

Michael A. Greene, Ph.D.
Directorate for Epidemiology and Health Sciences
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

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1. Introduction

The purpose of the statistical analysis is to provide estimates for exposure of children up to 26 months of age from diisononyl phthalate (DINP), a chemical found in polyvinyl chloride toys and other children's products.

Exposure, in this paper, was estimated from the product of migration rates from toys and other products, M , given in mass per unit time, and D , the duration or length of time that such products are likely to be in children's mouths. This was then divided by body weight, BW , to form equation (1),

$$(1) \quad DE = \frac{(M)(D)}{BW}$$

See Babich (1998).

Migration rates were estimated from the product of two other quantities, R and S , where R was the migration rate measured *in vitro* from product samples containing DINP and S was a scaling factor obtained from paired *in vitro* and *in vivo* studies using adult volunteers. The procedures used to obtain these measurements are described in Chen (1998). The exposure duration, D , in equation (1) was estimated from observations on toy mouthing behavior on children aged 3-26 months provided by Bea Steenbekkers from Wageningen Agricultural University. Tables developed from these data were published in the European Union's Consensus Report on DINP (Konemann, 1998) and in the full report Groot et al (1998a).

In the statistical analysis leading to estimates of exposure, the migration rate components, R , and S , and the exposure duration, D , were considered to be random variables, that is, quantities that vary over specimens, and individuals. What is the source of the random variation? First, some products, or different pieces of a single product could release DINP at different rates. Second, different human subjects would be expected to extract DINP from the same specimen at different rates. Taken together, the product $RS (=M)$ represents the variability in the amount of DINP in different toys and the rate it is released *in vivo*. Third, the variability in exposure duration, D , would reflect different amounts of time that children put objects in their mouths. This could vary by the age of the child, and for a given child could vary over short periods. Consequently, the daily exposure, DE , would vary between individuals, as the result of the amount of time they engage in chewing, sucking and licking of toys; the rate at which they extract DINP from the toys; and the DINP content of the toys in their environment.

In the analysis described in section 2 of this paper, separate lognormal distributions were fit to each of these random variables. One model was used for *in vitro* migration rates, M , and a second model for scaling, S . With respect to duration, D ,

separate estimates were made for children age 3-12 months and 13-26 months, because the amount of time these children were observed to engage in mouthing behavior was very different. Also, there were different values for mean body weight used for these different age groups.

Parameter estimates were obtained from the means and variances of the logarithms of the observed data. Statistical testing was used to test the goodness of fit of the data to the lognormal distributions.

The separate lognormal distributions were combined to form two lognormal distributions for *DE*, in equation (1), one for each age group. This was used to generate not only the geometric mean daily intake, but also the 95th percentile and the associated confidence interval for that statistic. The geometric mean is a typical measure of the center of a skewed distribution, and in fact, for the lognormal distribution, the geometric mean is an estimate for the median or 50th percentile of the data. The 95th percentile represents the DINP intake for the highest 5% of the children. This would represent children with the longest exposure to products with the greatest migration rates. Confidence intervals as shown in this analysis, represent the amount of uncertainty in the estimates. Confidence intervals for percentiles were from Hahn and Meeker (1991) and verified with parametric bootstrap calculations (Efron and Tibshirani, 1993). These are described in section 3 of the paper.

Section 4 contains a discussion of the results.

2. Fitting Statistical Distributions

This section describes the methods used to fit statistical distributions to the data. Section 2.1 describes fitting the *in vitro* migration rates, *R*. Section 2.2 discusses fitting the scaling distribution, *S*, and section 2.3 fits the exposure distributions to the data in Groot et al (1998b).

The mathematical form of the distributions used in fitting is the lognormal distribution, shown generically in equation (2). The distribution is defined only for positive values and displays a long right hand tail. Mathematically, if *X* is a random variable whose logarithm is normally distributed with parameters (μ, σ^2) , then *X* follows a lognormal distribution

$$(2) f(x) = \frac{1}{sx\sqrt{2p}} e^{-\frac{(\log x - m)^2}{2s^2}} \quad 0 < x < \infty, \quad -\infty < m < \infty, \quad s > 0$$

This is abbreviated $X \sim LN(\mu, \sigma^2)$.

The product of independent lognormal distributions also follows a lognormal

distribution. If $\log(X_1)$ and $\log(X_2)$ each follow a normal distribution then $\log(X_1) + \log(X_2) \sim N(\mu_1 + \mu_2, \sigma_1^2 + \sigma_2^2)$. Put another way, the product $X_1X_2 \sim LN(\mu_1 + \mu_2, \sigma_1^2 + \sigma_2^2)$. This result is very important because it allows finding the distribution of products of random variables such as found in equation (1) for daily exposure. Once the distribution of the products is available, estimates can be made for the geometric mean daily exposure and 95th percentiles. Closed form interval estimates for the mean and the percentiles are available from the fact that the distribution of means $(1/n_1)\sum\log(X_1) + (1/n_2)\log(X_2) \sim N(\mu_1 + \mu_2, \sigma_1^2/n_1 + \sigma_2^2/n_2)$ with $n_1 + n_2 - 2$ degrees of freedom. It is also interesting to note that exponentiating the mean of the underlying normal distribution is the geometric mean of the original data. Because the underlying distribution is symmetric, the geometric mean is also an estimate for the median of the original data.

The maximum likelihood estimates for the parameters of the lognormal distribution are found by taking the logs of the observations, then using maximum likelihood procedures for the normal distribution. This involves using the mean of the transformed data as the estimate for μ and the variance of the transformed data as the estimate for σ^2 . Exponentiating the estimate for μ (i.e. $\exp[\mu]$) produces a number in the original units that is the geometric mean of the data. (For further details on the lognormal distribution, see Casella and Berger, 1990).

2.1 Migration Rates

The distribution of migration rates for 31 products containing DINP is shown in table 1 below. The intent was to develop a list that would represent the range of toys containing DINP, that a child might put into his/her mouth. The data are the same as found in Table 4 of Chen (1998) except for deletion of four samples that did not contain DINP.

Examination of the histogram of migration rates showed that distribution has a skewed appearance with an arithmetic mean of 8.20, median of 4.8 and standard deviation (SD) of 9.83. The skewness statistic was 2.8. The Shapiro-Wilk W statistic (a test for the fit of the normal distribution) was 0.66 with a p value of less than 0.0001. Transforming to logs produced a mean of 1.66, median of 1.57, SD of 0.91, and a skewness statistic of 0.51. The Shapiro-Wilk W statistic, for the transformed data was 0.97 with a p value of 0.55. The skewness and normality test suggested that the log transformation was successful in fitting a normal distribution. Note that the mean value following the log transformation, corresponded to a geometric mean in the original data of 5.24.

Table 1
Distribution of DINP Migration Rates

Migration Rates	Frequency
0.0-2.4	5
2.5-4.9	13
5.0-7.4	4
7.5-9.9	1
10.0-12.4	2
12.5-14.9	2
15.0-17.5	1
17.5-	3
Total	31

Notes: The data are from Table 4 in Chen (1998) with four samples removed. Migration rates are given in micrograms per hour for an 11 square centimeter area. That size area was chosen because it was believed to be the same surface area as an object likely to be mouthed by a child.

There were some further analyses performed on these data. An analysis was conducted to determine if migration rates differed by type of specimen. Products were classified as teethingers, mouth toys, and others. To determine whether the data could be assumed to come from the same underlying process, a Kolmogorov-Smirnov test was performed on the empirical distributions of the migration rates by product classification. The p value for this test was 0.58, which did not provide any statistical justification for separating the analysis by type of product. This meant that there was no evidence to suggest that a particular product class had a greater migration rate than any other product type.

In a second analysis, models were estimated to determine if migration rates could be explained by the characteristics of the products. These characteristics included the percent DINP content by weight, the type of manufacturing process (e.g. injection molding, rotation, etc.) and the thickness of the product. The purpose of this analysis was to determine if there was some way to predict migration rates as related to the percent of phthalate content, manufacturing process, etc. While the graphical analysis showed some positive relationship between migration rate and DINP content, various regression models failed to produce a value of R^2 greater than 0.33. These models were judged to be inadequate to predict DINP migration rates especially given the shrinkage in predictive quality that would be expected from applying the models to new data. Moreover, discussions with CPSC laboratory staff suggested that migration rates were variable even within a single specimen.

2.2 Scaling Factors

To compute the scaling factors that would relate *in vitro* migration rates for the 31 products above to rates that would be expected from human mouthing, CPSC staff obtained migration data using 10 human volunteers. Details of this study are in Chen (1998). The testing used five duck toys that were identical to sample 2.02. Four disks were cut from each duck. Two disks from each toy were used for *in vivo* human subject testing and the remaining two were used for impaction. Each human provided measurements for four fifteen-minute periods for a total of 40 measurements. The data used in this analysis were those found in tables 5 and 6 of Chen (1998) but the *in vivo* and *in vitro* migration rates were divided by 10.3 to produce rates with units of micrograms per square centimeter per hour.

Like the migration rate data discussed above, these *in vivo* measurements also showed considerable skewness. The arithmetic mean was 25.0 micrograms per cm² per hour, with an SD of 16.7. The data were very skewed to the right with a skewness value of 1.46. The Shapiro-Wilk W statistic was 0.88 with a *p* value of 0.0004, confirming that the data did not follow a normal distribution. Transformation to logs provided a mean of 3.01 (geometric mean of 20.3) with a skewness of -0.5 and a value of W of 0.97 (*p* value of 0.5329).

An analysis of variance procedure (ANOVA) was applied to the migration rates to determine if there were any disk effects, gender effects or systematic variation in migration rates over the fifteen minute period. Using the log of the migration rate as the response variable, only the disk effect was statistically significant ($F = 3.85$ with 4 and 31 df, $p=0.0119$). On the basis of this analysis it was determined that even though the disks should have been identical, they should not be considered as replicates.

This information was used in determining how to obtain an average for the scaling factor. Let H_i and I_i denote average migration rates for disk i ($i = 1, 2, \dots, 5$), where H is the human average (two humans with 4 measurements each) and I is the machine impaction average (2 machine readings). Then the two possible ways to compute the average would be $S = \sum H_i / \sum I_i$ or $S = (1/5) \sum (H_i / I_i)$. The first approach is the ratio of the totals while the second is the average of the ratios. The second approach was used because the ANOVA showed that the ratios for each disk were significantly different from each other. If the human and machine observations could have been considered independent replicates, then the first calculation would be more appropriate.

The five ratios were 22.9, 32.3, 32.8, 54.6 and 72.6 with an arithmetic mean of 43.05 and an SD of 20.21. The data showed right skewness with a value of 0.85. The Shapiro-Wilk W statistic was 0.9040, ($p = 0.43$). These statistics did not strongly argue for a log transformation of the data, but because the analysis on the human extraction data above strongly suggested the log transformation for both the *in vivo* and *in vitro* migration rates, the ratios were also used in logarithmic form. Transforming to logs produced a mean of the logs of 3.68 (geometric mean 39.5) and SD of was 0.46. This improved the skewness to 0.46 and the Shapiro Wilk statistic to 0.9423 ($p = .6929$).

2.3 Exposure Analysis

In this last part of the statistical analysis, distributions were estimated for time children spent mouthing toys as reported in Groot et al (1998a, 1998b). Two separate analyses were conducted, one for children 3-12 months and the second 13-26 months. The 3-12 month period corresponds to the time when there is the highest mouthing activity for children and would be likely to result in the highest average daily intake of DINP. The children aged 13 to 26 months had spent much less time mouthing toys and would consequently have a much lower potential for exposure to DINP.

The age categories of 3-12 months and 13-26 months are similar to those in Groot et al (1998a). They reported using overlapping age boundaries (i.e. 3-6 months, 6-12 months, etc.), but inspection of the raw data showed that children at the lower end of the cell boundary were not contained in the particular age group. For example, a child age six months would have been in the 3-6 month group rather than the 6-12 month group. To avoid ambiguity, we characterize the cell boundaries as non-overlapping, so that we use 13-26 months in place of 12-26 months. Also, in this research, the upper boundary of 26 months is used rather than 36 months as reported in Groot et al (1998a). Inspection of the ages as reported in the raw data showed that there were only two children more than two years old, a 26 month old boy and a 35 month old boy. The remaining 9 children in that age category were between 19 and 24 months. Given the variability in the data, it seemed that one observation would be hardly sufficient to estimate the mouthing duration of children 27 months to 36 months, so this observation was omitted from the present reanalysis. Consequently the second part of the analysis only covers 13-26 months. No dosage estimates were made for children over 26 months.

Table 2 shows the data summarized by age group. Several aspects of this table were notable. First, duration was strongly related to age. For example, the two children aged 8 months averaged 78.3 minutes while children 14 months and over averaged 4 minutes or less. Second, not only were there ages where no children were observed, but also there were an unequal number of children observed at each age.

Table 2
Mean Toy Mouthing Time by Child Age

Age (months)	Number of Children	Mean Toy Mouthing Time (minutes)
3	1	12.6
4	2	8.6
5	2	21.8
6	0	-
7	2	42.8
8	2	78.3
9	4	15.7
10	3	25.0
11	1	0.4
12	2	5.1
13	2	9.1
14	1	4.0
15	1	3.8
16	2	4.0
17	2	2.8
18	4	1.1
19	2	0.9
20	0	-
21	3	0.5
22	3	2.5
23	0	-
24	1	0.0
25	0	-
26	1	1.3
27-34	0	-
35	1	0.0

Source: Groot, et al (1998a). Blanks indicate that there were no observations for children in those age categories.

The analyses for the 3-12 month old children and 13-26 months age children are described below.

2.31 3-12 Months

Table 2 shows that the maximum mouthing duration for toys occurred for children age 3 to 12 months. Even more important, the duration was substantially larger than for all other ages, with the maximum duration of 141.2 minutes provided by one of the two 8 month old subjects.

The arithmetic mean mouthing time for the 3-12 month age group was 24.4 minutes, the median was 15.3 and the standard deviation was 32.9. The skewness statistic was 2.85, with the Shapiro Wilk $W = 0.6530$ ($p < .0001$). As noted above, the largest observation was 141 minutes, followed by 70 minutes, 43 minutes and 31 minutes. The four smallest observations were 0.4, 1.8, 1.9 and 4.9 minutes. The extreme skewness suggested a log transformation of the data. The log transformed versions had corresponding statistics of mean = 2.49 and SD = 1.37. The value of the skewness statistic was = -0.6840. The Shapiro Wilk W was 0.9559 ($p = .4976$). From the transformed data, the geometric mean mouthing time was 12.03 minutes with an estimated 95% confidence interval of 6.2 to 23.3 minutes.

While these mouthing times may appear to be low, the data showed that children spent much more time mouthing other objects such as fingers and pacifiers. For 3-12 month old children the average usage of pacifiers was 45 minutes per day and fingers was 11 minutes per day. Mouthing times for pacifiers and other objects were not considered in the estimates for duration and DINP intake because they did not contain DINP. This is discussed in the appendix to this paper.

2.32 13-26 Months

This analysis used the same strategy as 3-12 months. The arithmetic mean mouthing time for children aged 13-26 months was 2.54 minutes with a median of 1.49 minutes, a SD of 2.94 minutes, skewness of 1.4117 and Shapiro Wilk W statistic of 0.8161 ($p = 0.0006$). This distribution was also highly skewed, suggesting the log transformation. The five largest observations were 10.4 minutes, 8.1 minutes, 7.7 minutes, 4.0 minutes and 3.9 minutes, while there were 5 values with zero recorded mouthing time. While the skewness and the very large observations again suggested a log transformation, the five zeroes proved to be worth consideration.

These five zero observations were from a child age 16 months, 2 children at 18 months, one at 19 months, and one at 24 months. One possibility would be to replace them with very small quantities, however this would induce negative skewness, that is, it would create the opposite outlier problem as found with the original values. This strategy was rejected. The remaining two approaches were (1) dropping the 5 cases with zeroes and then transforming to logs and (2) averaging the observations by month of age, before taking the logs. This second strategy had the desired result of reducing the number of zeroes to one for the child age 24 months, but at the cost of artificially lowering the standard deviation of the data.

The first approach of dropping the zeroes before transforming to logs, produced a mean of 0.74, an SD of 1.06, skewness of -0.3176, and Shapiro Wilk $W = 0.7372$ ($p = .2875$). Averaging ages before taking logs produced a mean of 0.77, an SD of 0.88, skewness of -0.8850 and Shapiro Wilk $W = 0.9620$ ($p = .7964$). Because the means were

very close for both approaches, and because averaging first had the undesirable effect of lowering the SD, the first approach of dropping the zero observations was selected. Using this approach, the geometric mean was estimated at 2.1 minutes with a 95% confidence interval of 1.22 to 3.62 minutes.

3. Estimates for Average Daily Exposure

Equation (1) can be reexpressed in logarithmic terms as (3) $\log(DE) = \log(M) + \log(D) - \log(BW)$

where DE = daily oral exposure, M is migration rate per unit time, D is exposure duration and BW is body weight. Parameter estimates for that model are found in table 3 below.

Table 3
Estimates for Log of Average Daily Exposure for a child 3-12 months
(micrograms per day per 10 kg BW)

Component	Mean	Variance	Sample Size
Migration Rate (M)	1.6565	0.8318	31
Scaling Factor (S)	3.6766	0.2120	5
Exposure (D)	2.4880	1.8695	19
Constants	-6.0822	0.0000	-
Log of Average Daily Exposure (DE)	1.7389	2.9133	-

Notes: See section 2 for parameter estimates. Constants are $-\text{Log}(7.3)$ to convert the resulting exposure per kilogram to exposure per 7.3 kg (mean body weight) and $-\text{Log}(60)$ to convert from minutes to hours. The average body weight was from Snyder et al (1977). Constants enter additively for logarithmic relationships. The variance is calculated conventionally for M and S and D and described above.

Table 3 shows the log of average daily exposure for a child 3-12 months old. As noted above, these data are assumed to follow a lognormal distribution with parameters, $\mu = 1.7389$ $\sigma^2 = 2.9133$ ($\sigma = 1.7069$). Exponentiating the results provides an estimate of the geometric mean of 5.69 micrograms per 7.3 kg child per day, with a 95% confidence interval of (2.5 to 12.9) micrograms.

The point estimate for the 95th percentile is $\exp(\mu + 1.65\sigma/\sqrt{n})$, which is essentially the same as that for a normal distribution except that the result is exponentiated. The interval estimate for the 95th percentile follows Section 4.4 in Hahn

and Meeker (1991), who provide an interval estimate for the percentile of a normal distribution, and also associated tables. The underlying theory, according to them, involves the noncentral t distribution. To check these intervals, parametric bootstrap confidence intervals were also created (Efron and Tibshirani, 1993). These were very close to the intervals in Hahn and Meeker.

The 95th percentile exposure was 94.3 micrograms with a 95% confidence interval of (50.1 to 225.6).

Table 4 contains values for a child 13-26 months in the same units.

Table 4
Estimates for the Log of Average Daily Exposure for a child 13-26 months
(micrograms per day per 10 kg BW)

Component	Mean	Variance	Sample Size
Migration Rate (M)	1.6565	0.8318	31
Scaling Factor (S)	3.6766	0.2120	5
Exposure (D)	0.7447	1.1185	17
Constants	-6.4246	0.0000	0
Log of Average Daily Exposure (DE)	-0.3868	2.1623	-

Notes: See section 2 for parameter estimates and the notes for table 4. The variance is calculated the same way as table 4. The average body weight used was 10.7 kg (Snyder et al, 1977).

Exponentiating the results in table 4 produced a geometric mean daily exposure of 0.69 micrograms per 10.7 kg per day, with a 95% confidence interval of (0.32 to 1.55). The estimated 95th percentile exposure was 7.6 micrograms with a 95% confidence interval of 4.4 to 16.2 micrograms.

4. Conclusion

This paper has described the method for estimating DINP intake used for children aged 3-12 months and 13-26 months. The approach is similar to that taken by the Dutch Consensus group (van Veen, 1998). Migration rates were developed from in-vitro experiments, then scaled by using migration rate data from paired in-vitro and in-vivo samples. Mouthing durations were obtained from Groot et al (1998a).

These data were combined into an analytic model that used a lognormal distribution for human exposure duration, combining estimates from the separate experiments. Geometric means, 95th percentiles and associated confidence intervals

were estimated.

The results showed a geometric mean average daily intake of 5.7 micrograms per day (95% confidence interval 2.5 to 12.9) for children between ages 3 and 12 months. The distribution was very skewed, with an estimate of 5% of children at 94.3 micrograms or more (95% confidence interval 50.1 to 225.6). The values for children at 13-26 months was considerably lower with a geometric mean of less than 1 microgram per day.

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Appendix

Differences between CPSC research and the Dutch Consensus Group Report

This paper differs from the research by the Dutch Consensus group in the following respects:

1. The Dutch Consensus group used three specimens cut from two products for DINP extraction while we used specimens from 31 different products.
2. Instead of using machine impaction methods and then scaling them with paired *in vitro* and *in vivo* measurements, the Dutch Consensus group obtained migration rates directly from 20 adult human subjects using these three specimens (Meuling and Rijk, 1998).
3. Instead of fitting a probability distribution for migration rates or exposure duration, the Dutch consensus group used a Monte Carlo simulation that sampled from the empirical distribution of migration rates and exposure durations.
4. The Dutch consensus group used a normal distribution for body weight in their simulation, assuming age specific values ranging from 6.25 kg for children 3-6 months to 13.5 kg for children 18-36 months. The analysis in this paper used a constant 7.3 kg body weight for children aged 3-12 months and 10.7 kg for children 13-26 months.
5. Exposure durations used in our analysis were restricted to those from objects labelled as “Mouth Toys” or “Other Toys,” in Groot et al (1998a), while the Dutch Consensus group reported using the larger quantity of “all mouthing activities except sucking on dummies (also known as pacifiers).” See van Veen (1998).

The most important distinctions would result from items 1 and 5 above. With respect to item 1, the migration rate estimates, the Dutch Consensus group used three specimens (see Meuling and Rijk, 1998). The first specimen was a standard PVC sample containing 38.5% DINP and was not a consumer product. The second and third were sections from a teething ring; specimen 2 was a “finger,” and specimen 3 was from a flat part of the same toy. In contrast we used specimens from 31 different products, including toys and teething rings, with DINP content varying from 15 to 54% (see Chen, 1998, table 4). These products were chosen from toys we believed were likely to be sucked, chewed or mouthed by children.

The other important distinction is item 5 above. While we and the Dutch Consensus group used the same source for the exposure duration, (Groot, et al, 1998b), the Dutch consensus group used total mouthing time for all objects other than pacifiers as an estimate for the time that children would be exposed to DINP. Total mouthing time included observations for children mouthing their fingers and also objects defined as non toys (cloth, cutlery, paper, adult books). See Groot et al, (1998b, appendix 1). The statistical analysis in this paper used only reported mouthing time for toys, which included the two categories of “toys for mouthing,” and “other toys.” The difference is

substantial. For example, for age group 6-12, the mean mouthing duration was reported as 27.9 minutes for toys and 44 minutes for all objects (Groot, et al, 1998b table 5-13). Resulting, total mouthing time overstates the mean toy mouthing time by a factor of 58 percent. Since fingers and non toys did not contain DINP, it did not appear appropriate to use total mouthing time.

It is doubtful that the differences from items 2, 3 and 4 above would be substantial. There has been much research on different methods for measurement of DINP migration rates and there is still much to be learned about variability inherent in different laboratory methods (see Chen, 1998). In item 3, the use of a Monte Carlo simulation instead of the fitting of analytic models, the difference would turn on how well the models fit the data. If the models fit well, then a large number of Monte Carlo samples would have about the same results as the analytic models. We preferred to use an analytical model whenever possible for analytic tractability and to facilitate obtaining confidence intervals.

Finally, the use of variable body weights instead of a fixed constant of 7.3 or 10.7 kg would be unlikely to make much difference because the variability in body weight would be small, compared to the other sources of variability in these analyses.