Do interspecies correlation estimations increase the reliability of toxicity estimates for wildlife?

Laura Golsteijn*[1], Harrie W.M. Hendriks[1,2], Rosalie van Zelm[1], Ad M.J. Ragas[1,3], and Mark A.J. Huijbregts[1]

[1] Department of Environmental Science, Radboud University, P.O. Box 9010, 6500 GL Nijmegen, The Netherlands

[2] Department of Applied Stochastics, Radboud University, P.O. Box 9010, 6500 GL Nijmegen, The Netherlands

[3] Open University, School of Science, P.O. Box 2960, 6401 DL Heerlen, The Netherlands

* To whom correspondence may be addressed
Email: L.Golsteijn@science.ru.nl
Phone: + 31 (0)24 365 20 66
Fax: + 31 (0)24 355 34 50

Email addresses contributing authors:
Harrie W.M. Hendriks: Harrie.Hendriks@math.ru.nl
Rosalie van Zelm: R.vanZelm@science.ru.nl
Ad M.J. Ragas: A.Ragas@science.ru.nl
Mark A.J. Huijbregts: M.Huijbregts@science.ru.nl

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ABSTRACT

For warm-blooded species, the hazardous dose of a chemical (HD50) is an upcoming and important characteristic in the assessment of toxic chemicals. Generally, experimental information is available for a limited number of warm-blooded species only, which causes statistical uncertainty. Furthermore, when small datasets contain an unrepresentative sample of species, they can cause systematic uncertainty in chemicals' hazardous doses. The number of species can be enlarged with interspecies correlation estimation (ICE) models, but these are uncertain themselves. The goal of this study is to quantify the possible gain in reliability of the HD50 values for warm-blooded wildlife species after enlargement of the sample size with ICE predictions. For 1137 chemicals, we compared systematic uncertainty and statistical uncertainty between HD50 values based on experimental data ($HD50_{Ex}$) and on datasets combining experimental data and ICE predictions ($HD50_{Co}$). $HD50_{Ex}$ values ranged between $1.0 \cdot 10^{-1}$ and $9.5 \cdot 10^{3}$ $mg \cdot kg_{wwt}^{-1}$, and $HD50_{Co}$ values between $1.1 \cdot 10^{0}$ and $6.1 \cdot 10^{3}$ $mg \cdot kg_{wwt}^{-1}$. For over 97 percent of the chemicals, $HD50_{Ex}$ values exceeded $HD50_{Co}$ values, with a systematic uncertainty (i.e. the ratio of $HD50_{Ex}/HD50_{Co}$) of typically 3.5. The limited availability of experimental toxicity data, predominantly for mammals, resulted in a systematic underestimation of the wildlife toxicity of a chemical. Statistical uncertainty factors (i.e. the ratio of the $95^{th}/5^{th}$ percentile) quantified the statistical uncertainty in the HD50 values. The statistical uncertainty factors ranged between $1.0 \cdot 10^{0}$ and $2.5 \cdot 10^{22}$ for the experimental dataset, and between $4.8 \cdot 10^{0}$ and $1.1 \cdot 10^{2}$ for the combined dataset. For all sample sizes, median statistical uncertainty factors were the largest for combined datasets. However, combining experimental toxicity data with ICE predictions makes it possible to reduce the upper limit of the range for statistical uncertainty factors. We conclude that, by combining experimental data with ICE model predictions, the validity of the HD50 value can be improved and high statistical uncertainty can be reduced, particularly in cases of limited

toxicity data, i.e. data for mammals only or a sample size of $n \leq 4$. **Keywords** – hazardous dose (HD50), toxicity estimates, uncertainty, interspecies correlation estimations, warm-blooded species

1. INTRODUCTION

Several sample statistics are used to describe the toxicity of chemical exposure and uptake. One of them is the dose or environmental concentration of a chemical toxic to at least 50 percent of the individuals in 50 percent of all species. This hazardous dose or concentration (HD50 or HC50, respectively) is estimated by the median from all available species-specific LD50 or LC50 values. It implies that at least 50 percent of the individuals in 50 percent of all species is expected to be protected against the chemical's toxic effects. In the Sediment Quality Triad concept (Long and Chapman, 1985), the HC50 is used in the integrated use of site-specific chemical, toxicological and ecological information. In addition, Kooijman (1987) and Luttik and Aldenberg (1997) suggested that by applying safety factors to the HD50 or HC50, a hazardous dose or concentration for sensitive species can be derived. In life cycle impact assessment, the HD50 and HC50 are directly applicable, because a median estimate for the effect of chemicals is used (Hauschild, 2005). Van de Meent and Huijbregts (2005) explained how life cycle assessment effect factors can be calculated from the median toxicity value. Somewhat simpler is the linear approach recommended by Pennington et al. (2004), which has also been used to calculate effect factors for warm-blooded species from the HD50 (Golsteijn et al., 2012). In this study, we focus on warm-blooded species only. Since the HD50 is an upcoming and important characteristic in the assessment of toxic chemicals, it is of great importance to know not only its absolute value but also its uncertainty.

The size of the uncertainty in the HD50 is directly determined by, among other things, the number of species in the HD50 sample (Luttik and Aldenberg, 1997). Usually, the sample size is small. Larsen and Hauschild (2007) and Henning-de Jong et al. (2009) emphasized the importance of finding an optimal method for making best estimates of toxicity based on small

datasets. In this paper, we will refer to the uncertainty caused by small sample sizes as statistical uncertainty. Furthermore, when small datasets contain an unrepresentative sample of species, they can cause systematic uncertainty in chemicals' hazardous doses. For the estimation of hazardous doses for warm-blooded species, mammals and birds are grouped (resembling Posthuma et al., 2002; Golsteijn et al., 2012). However, experimental tests are frequently based on a small number of mammalian species, even though birds are suggested to be more sensitive to chemicals (Schafer, 1972; McConnell, 1985; Van der Wal et al., 1995).

The sample size can be enhanced by increasing the number of laboratory experiments, which is expensive and ethically controversial. Quantitative structure-activity relationships between chemicals (QSARs) have also been used for effect estimates in chemical risk assessment (e.g. Devillers and Devillers, 2009). As an additional approach, interspecies correlation estimation (ICE) models have been developed to estimate the toxicity of chemicals. These models have been used by Asfaw et al (2003), Awkerman et al (2008; 2009), and Raimondo et al (2007) to develop SSDs for wildlife species for a range of chemicals. With ICE models, acute toxicity values of a chemical to multiple species can be predicted from a single experimental acute toxicity value of the chemical to a so-called surrogate species (Asfaw et al., 2003). However, the introduction of estimated effect data brings extra uncertainty in the HD50 input data. It is unknown whether this extra uncertainty outweighs the uncertainty caused by a small experimental sample size.

The goal of this study is to quantify the possible gain in reliability of the HD50 values for warm-blooded wildlife species after enlargement of the number of species with ICE model predictions. We studied systematic uncertainty and statistical uncertainty in HD50 values in relationship with sample size.

105

106 ## 2. METHODOLOGY

107

108 ### 2.1 Hazardous dose

109 The hazardous dose of a chemical x ($HD50_x$) was estimated by the geometric mean of the
110 log-normally distributed LD50 values (i.e. the oral doses of chemical x that are expected to
111 kill 50 percent of the individuals in a given population). Therefore, log $HD50_x$ equals the
112 arithmetic mean of the log-transformed LD50 values (quantified as unit of chemical weight
113 per unit of species wet weight, i.e. $mg \cdot kg_{wwt}^{-1}$):

114 $$\log HD50_x = \frac{1}{n} \cdot \sum_{i=1}^{n} \log LD50_{i,x} \quad (1)$$

115 where n is the number of warm-blooded species for which toxicity data are available, and
116 $LD50_{i,x}$ is the oral dose of chemical x that is lethal to 50 percent of the individuals of species i
117 ($mg \cdot kg_{wwt}^{-1}$). A comparison was made between HD50 values based on experimental data only
118 ($HD50_{Ex}$), and on a combined dataset of experimental values and ICE estimates ($HD50_{Co}$).
119 For the calculations of $HD50_{Co}$, experimental data were preferred over model predictions (see
120 Figure 1).

121

122 ### 2.2 Experimental data

123 Oral LD50 values were obtained from experimental studies reported in the Registry of
124 Toxic Effects of Chemical Substances (RTECS, Accelrys Inc., 2011), taking into account
125 three criteria. First of all, in order to prevent dependency between the effect dataset used for
126 derivation of the ICE models (Raimondo et al., 2010) and the effect data used in this study,
127 we excluded data for chemicals that were present in the ICE model dataset. Secondly, toxicity
128 values indicating ranges or > and < values were not included. Finally, per chemical,
129 experimental LD50 values should be available for at least two species of which at least one

could function as a surrogate species in the ICE models from Raimondo et al. (2010). In case there were multiple toxicity values available for the same species, we used the geometric mean. In the end, our dataset consisted of 1137 chemicals.

2.3 Interspecies Correlation Estimation

We used the ICE models available from Raimondo et al. (2010), in order to enhance the dataset of experimental LD50 values. The ICE statistical models are log-linear least square regression models (Asfaw et al., 2003). The slope (b) and intercept (a) for each ICE-regression were derived from the equation:

$$\log(LD50_{j,x}) = a + b \cdot \log(LD50_{i,x}) \quad (2)$$

where $LD50_{j,x}$ refers to the predicted toxicity value of chemical x for species j, and $LD50_{i,x}$ refers to the toxicity value of chemical x for surrogate species i. The ICE models were applied only within the toxicity range they were derived from by Raimondo et al. (2010). As RTECS (Accelrys Inc., 2011) gives acute toxicity data on a genus level and the ICE models from Raimondo et al. (2010) require implementation on a species level, we used RTECS toxicity values for the most commonly used test species. Hence, rat toxicity values were used for surrogate species 'Rattus norvegicus', pigeon toxicity values for 'Columba livia', duck toxicity values for 'Anas platyrhynchos', and quail toxicity values for 'Coturnix japonica'. For species' toxicity values that could be predicted from more than one surrogate species, we chose the prediction with the lowest standard deviation.

2.4 Systematic uncertainty

We estimated HD50 values based on experimental data only, and on a combined dataset of experimental values and ICE predictions, and calculated systematic uncertainty as follows:

$$UF_{sys,x} = HD50_{Ex,x} / HD50_{Co,x} \quad (3)$$

in which $UF_{sys,x}$ is the systematic uncertainty factor for the hazardous dose of chemical x, $HD50_{Ex,x}$ and $HD50_{Co,x}$ are the hazardous doses for chemical x based on the experimental dataset and the combined dataset, respectively. We calculated the systematic uncertainty for datasets including all wildlife species for which data were available (i.e. mammals and birds), and for datasets with only mammalian data.

2.5 Statistical uncertainty

We quantified the statistical uncertainty separately for the HD50 values based on experimental toxicity values and on a combination of experimental and predicted toxicity data. In both cases, statistical uncertainty in the HD50 values was quantified by an Uncertainty Factor, based on the 90% confidence interval (CI) of the log HD50 values. To be exact, we described the uncertainty in the log HD50 predicted from a sample with normally distributed log LD50 values and unknown variance (Roelofs et al., 2003). Subsequently, we calculated a statistical uncertainty factor ($UF_{stat,x}$) according to:

$$UF_{stat,x} = P_{0.95} / P_{0.05} = 10^{2 \cdot t_{0.90} \cdot SEM_x} \quad (4)$$

were $P_{0.95}$ and $P_{0.05}$ are the 95th- and 5th-percentile of the log $HD50_x$ distribution, $t_{0.90}$ is the value of the t-distribution for the log $HD50_x$ that corresponds to the 90% CI depending on the degrees of freedom, and SEM_x is the standard error of the log $HD50_x$.

Experimental Dataset – The standard error of the log $HD50_x$ based on experimental data only ($SEM_{Ex,x}$) was calculated according to:

$$SEM_{Ex,x} = \sqrt{s^2_{Ex,x} / n} \quad (5)$$

in which

$$s^2_{Ex,x} = \frac{1}{n-1} \sum_{i=1}^{n} (\log LD50_{i,x} - \log HD50_{Ex,x})^2 \quad (6)$$

In these equations, $s^2_{Ex,x}$ is the variance of the experimental log LD50 values for chemical x; n is the number of experimental $LD50_x$ values in the $HD50_x$ calculation; $LD50_{i,x}$ are the LD50 values for chemical x per experimentally tested species i; and $HD50_{Ex,x}$ is the hazardous dose for chemical x in the experimental dataset.

Combined Dataset – For the combination of experimental and predicted toxicity data, the standard error of the log HD50 ($SEM_{Co,x}$) was calculated according to:

$$SEM_{Co,x} = \sqrt{\frac{s^2_{Co,x}}{n+m} + \frac{m^2}{(n+m)^2} s^2_{ICE,x}} \quad (7)$$

in which

$$s^2_{Co,x} = \frac{1}{n+m-1} \sum_{i+j=1}^{n+m} (\log LD50_{Co,x} - \log HD50_{Co,x})^2 \quad (8)$$

$$s^2_{ICE,x} = \left(\frac{1}{m} \sum_{j=1}^{m} s_{j,x} \right)^2 \quad (9)$$

In these equations, $s^2_{Co,x}$ is the variance of all log LD50 values available for chemical x, both tested and predicted; n is the number of experimental $LD50_x$ values in the $HD50_x$ calculation; m is the number of predicted $LD50_x$ values in the $HD50_x$ calculation; $s^2_{ICE,x}$ is the squared average regression error of the ICE models used for predicting the log LD50 of chemical x; $LD50_{Co,x}$ is the experimentally tested (i) or predicted (j) toxicity value of chemical x; $HD50_{Co,x}$ is the hazardous dose of chemical x for the combined dataset; and $s_{j,x}$ is the standard deviation of the predicted log LD50 for chemical x in species j, calculated according to Mendenhall and Beaver (1994). For the calculation steps of $s_{j,x}$, we refer to the supporting information (par. 1.2). Equation 9 holds for situations in which the residual errors in the ICE-predictions are fully correlated (r=1), and is further explained in the supporting information (par 1.2).

3. RESULTS

We calculated hazardous doses for a set of 1137 chemicals. HD50 values ranged between $1.0 \cdot 10^{-1}$ and $9.5 \cdot 10^{3}$ $mg \cdot kg_{wwt}^{-1}$ for the experimental data, and between $1.1 \cdot 10^{0}$ and $6.1 \cdot 10^{3}$ $mg \cdot kg_{wwt}^{-1}$ for the combined dataset. HD50 values from experimental datasets exceeded the ones from combined datasets for over 97 percent of the chemicals, with a systematic uncertainty factor of typically 3.5. **Figure 2a** shows that, in general, we observed an increase in the systematic uncertainty of chemicals' hazardous doses as the $HD50_{Ex}$ value increased. For the small cloud of data points in the top right, the sample sizes of the $HD50_{Co}$ values were all smaller than eight species. Including only LD50 values tested or modeled for mammalian species, this trend was generally not observed (see **Figure 2b**). However, in Figure 2b two separate clouds of data points can be observed. The lower group represents $HD50_{Ex}$ values based on a median sample size of n=3 and $HD50_{Co}$ values based on a median sample size of n=10. For the upper group the difference in sample size is much smaller, as $HD50_{Ex}$ and $HD50_{Co}$ values were based on median sample sizes of n=2 and n=5, respectively.

Obviously, the sample sizes of the different datasets differed to a large extent. The datasets with experimental effect data contained toxicity values per chemical for 2 to 11 warm-blooded species (median n=2). Rat and mouse LD50 values were available for 98 and 91 percent of the chemicals, respectively. For less than 6 percent of the chemicals there was at least one LD50 value for birds available. With both experimental values and ICE predictions, the datasets contained toxicity values per chemical for 3 to 43 species (median n+m=21). Less than 0.3 percent of the chemicals had no LD50 values for birds in their combined dataset. **Figure 3a** shows that the systematic uncertainty of a chemical's hazardous dose decreased as the number of species for which toxicity was tested increased. We did not

find a similar trend for systematic uncertainty if we included only LD50 values tested or modeled for mammalian species (see **Figure 3b**).

We compared the statistical uncertainty factors of the hazardous doses from experimental and combined datasets. We observed a large difference in the ranges of UF_{stat} values between the experimental and the combined dataset. The statistical uncertainty factors ranged between $1.0 \cdot 10^{0}$ and $2.5 \cdot 10^{22}$ for the experimental dataset, and between $4.8 \cdot 10^{0}$ and $1.1 \cdot 10^{2}$ for the combined dataset (see SI par. 2.1). For experimental datasets, UF_{stat} values ranged, for instance, twenty-two orders of magnitude for n=2 and four for n=4 (see SI par. 2.1). **Figure 4** illustrates the influence of the number of species in the experimental dataset on the uncertainty factor. For both $HD50_{Ex}$ and $HD50_{Co}$ values we observed that the statistical uncertainty decreased with increasing numbers of species included in the HD50 calculations. For all sample sizes, median statistical uncertainty factors were the largest for combined datasets. However, combining experimental data with ICE predictions makes it possible to reduce the upper limits of the uncertainty factor ranges.

4. DISCUSSION

In this study, we calculated hazardous doses for warm-blooded species based on experimental data and on a combined dataset of experimental values and model predictions. Here, we discuss the interpretation of our findings, including the uncertainties associated with our methodology, and the conclusions.

For over 97 percent of the chemicals, HD50 values from experimental datasets exceeded the ones from the combined dataset. This finding was related to the low diversity of species for which toxicity values were available. Laboratory experiments are predominantly

250 performed on rodent species, in particular rats and mice, because of, among other things, their
251 manageability under laboratory conditions. Our experimental dataset also contained mainly
252 rodent data. Awkerman et al. (2009) showed rodents are most often in the least sensitive
253 quartile of species sensitivity distributions. Moreover, several authors suggest that birds may
254 be more sensitive than mammals for the effects of chemical exposure (Schafer, 1972;
255 McConnell, 1985; Van der Wal et al., 1995). For example, Van der Wal et al. (1995)
256 concluded from a principal component analysis of a combined dataset of birds and mammals
257 that there is a clear difference in sensitivity between classes. Their analysis showed that
258 although within each class the magnitude of the differences in sensitivity is similar, as a
259 group mammals are less sensitive than birds. These studies all point out that, as a group, birds
260 are the most sensitive wildlife species. In line with that, Figures 2b and 3b show barely
261 systematic uncertainty between $HD50_{Ex}$ values and $HD50_{Co}$ values if we only included
262 mammalian toxicity data, illustrating the importance of including avian toxicity data in the
263 estimation of a HD50 for warm-blooded species. Furthermore, in figure 2b, we observed two
264 separate clouds of data points, showing how $HD50_{Co}$ values approach $HD50_{Ex}$ values closer if
265 their samples sizes do not deviate too much. This finding suggests that even within the group
266 of mammals, systematic uncertainty can be present if the sample size is too small and the
267 diversity of species too low.

268 For both experimental and combined datasets, we observed a reduction in statistical
269 uncertainty with increasing numbers of species included in the HD50 calculations. Other
270 authors found as well that the number of species tested per chemical is a dominant factor in
271 the uncertainty distributions of median toxicity values for both warm-blooded species (Luttik
272 and Aldenberg, 1997) and cold-blooded species (Aldenberg and Jaworska, 2000; Pennington,
273 2003; Harbers et al., 2006; van Zelm et al., 2007; Van Zelm et al., 2009). E.g., Van Zelm et
274 al. (2007) studied the ranges in statistical uncertainty factors of the median lethal

concentrations of high production volume chemicals. They found twenty-five orders of magnitude for n=2 reducing to five orders of magnitude for n=4. We showed that the combination of experimental and predicted data reduces the upper limit of the range for statistical uncertainty factors, in cases of limited experimental toxicity data ($n \leq 4$).

As is shown in Figure 4, statistical uncertainty does not decrease for all chemicals by including interspecies correlation predictions. However, small experimental samples frequently consist of relatively closely related rodents, and are therefore likely to show a smaller spread in LD50 values than relatively large samples with a higher diversity in species. Due to this bias in sample composition, small experimental samples may underestimate statistical uncertainty. Therefore, enhancement of experimental toxicity datasets with ICE predictions may actually result in more prominent reductions of statistical uncertainty than what was found in this study.

5. CONCLUSION

We compared HD50 values based on experimental data only and on a combined dataset of experimental values and ICE predictions, and looked at systematic and statistical uncertainty of chemicals' hazardous doses. We found that the limited availability of experimental toxicity data, predominantly for mammals, resulted in a systematic underestimation of the wildlife toxicity of a chemical. This emphasizes the importance of including avian toxicity data in the estimation of a HD50 for warm-blooded species. Consequently, we recommend including toxicity data of both mammals and birds in risk assessments or life cycle impact assessments where HD50 values for warm-blooded wildlife species are used. We conclude that, by combining experimental data with ICE model predictions, the validity of the HD50 value can

be improved and high statistical uncertainty can be reduced, particularly in cases of limited toxicity data, i.e. data for mammals only or a sample size of $n \leq 4$.

Supplementary data – the supplementary data provides details about the uncertainty calculations. It also gives the complete list of HD50 values based on experimental and combined datasets, together with the statistical and systematic uncertainty factors.

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415 percentile, and the whiskers the 5th and 95th percentiles. In the columns, the
416 median UF_{stat} value is marked. N is the number of chemicals.