Beyond Science and Decisions: From Problem Formulation to Dose-Response

Case Study Proposals

Austin, Texas
March 16-18, 2010

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail: ACC ARASP Center

1. **Please identify the issue/problem formulation that the proposed method aims to address (*e.g.*, Screening level assessment).**

   Review cases in which substance-specific data has been used *in lieu* of defaults and "catalog the principles characterizing those departures. The principles can be used in developing more general guidance for deciding when data clearly support an inference that can be used in place of a default."

   If the default approach is determined to not be appropriate, then an alternative approach may be developed.

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   See the examples.

3. **Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

   Thyroid Follicular Tumors
   "Consider, for example, EPA's guidance for chemicals that cause follicular tumors. Section 2.2.4 of EPA 1998b (p. 21) requires that "enough information on a chemical should be given to be able to identify the sites that contribute the major effect on thyroid-pituitary function," but EPA does not indicate what quantity and quality of information are "enough" for a researcher to make such a determination. In addition, the key statement that "where thyroid-pituitary homeostasis is maintained, the steps leading to tumor formation are not expected to develop, and the chances of tumor development are negligible" refers throughout the document to humans in general and does not address inter-individual variability in homeostasis." – As discussed in the Silver Book.

   Or Boron
   BOX 6-1
   Boron: Use of Data-Derived Uncertainty Factors

   As described in the Silver Book:

   "EPA has been struggling with characterization of uncertainty in risk assessments for decades. In most cases involving noncancer health effects, default uncertainty factors are used to account for conversion of subchronic to chronic exposure data, the adequacy of the database, extrapolation from the lowest-observed-adverse-effect level to a no-observed-adverse-effect level, interspecies extrapolation, and human variability. Inadequacies in the

database often compel the agency to rely on default assumptions to compensate for gaps in data. In the case of the boron risk assessment, data were available, so EPA could apply a "data-derived approach" to develop uncertainty factors. This approach "uses available toxicokinetic and toxicodynamic data in the determination of uncertainty factors, rather than relying on the standard default values" (Zhao *et al*., 1999). – As discussed in the Silver Book. The boron case illustrates issues surrounding the development and use of data-derived uncertainty factors by the agency.

"Without endorsing the specifics, the committee notes that in the boron risk assessment the availability of data lowered the uncertainty factor by roughly one-third, from 100 to 66. Chemical-specific pharmacokinetic and physiologic data were used to derive the factors (DeWoskin *et al.,* 2007). Specifically, data on renal clearance from studies of pregnant rats and pregnant humans were used in determining data-driven interspecies pharmacokinetic adjustments, and glomular-filtration variability in pregnant women was used to develop the nondefault values for intraspecies pharmacokinetic adjustments.

"The data-derived approach used in the risk assessment was largely supported by the three external reviewers of the risk assessment (see EPA 2004; p. 110): All three reviewers agreed that the new pharmacokinetic data on clearance of boron in rats and humans should be used for derivation of an uncertainty factor instead of a default factor. Comments included statements that EPA should always attempt to use real data instead of default factors and a statement that this use of clearance data is a significant step forward in the general EPA methodology for deriving uncertainty.

"The use of data-driven uncertainty factors was not without controversy, as reported in a 2004 *Risk Policy Report*: "environmentalists are concerned EPA is eroding its long-standing practice of using established safety factors when faced with scientific uncertainties. 'Our major concern is that this represents a major move by EPA away from the concept of defaults, and towards a concept of default if we think that it's required, and if there are data to support a default','' a scientist with the Natural Resources Defense Council says. "EPA may use a 'scrap of evidence' to support the idea that one chemical is like another, reducing the need for important safety factors, the source says" (Risk Policy Report, 2004, p. 3)."

4. Proposed team to develop case study (desired, but optional)

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References

DeWoskin, R.S., J.C. Lipscomb, C. Thompson, W.A. Chiu, P. Schlosser, C. Smallwood, J. Swartout, L. Teuschler, and A. Marcus. 2007. Pharmacokinetic/physiologically based pharmacokinetic models in integrated risk information system assessments. Pp. 301-348 in Toxicokinetics and Risk Assessment, J.C. Lipscomb, and E.V. Ohanian, eds. New York: Informa Healthcare.

EPA (U.S. Environmental Protection Agency). 2004. Exposure and Human Health Reassessment of 2,3,7,8- Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds,

NAS Review Draft. EPA/600/P-00/001Cb. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental

Protection Agency, Washington DC [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=87843.

Risk Policy Report. 2004. EPA Boron Review Reflects Revised Process to Boost Scientific Certainty. Inside EPA's Risk Policy Report 11(8):3.

Zhao, Q., J. Unrine, and M. Dourson. 1999. Replacing the default values of 10 with data-derived values: A comparison of two different data-derived uncertainty factors for boron. Hum. Ecol. Risk Asses. 5(5):973-983.

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1. **Please identify the issue/problem formulation that the proposed method aims to address (*e.g.*, Screening level assessment).**

   Evaluating the recommended default for inter-individual variability in cancer susceptibility (Silver Book, Page 168-169)

   The evaluation will consist of a critical review of the methodology, evaluation of the assumptions and models, and discussion of whether the underlying biological processes do or do not support adopting such a default approach.

   If the default approach is determined to not be appropriate, then an alternative approach may be developed.

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   Silver Book Recommended Default for Inter-individual Variability in Cancer Susceptibility

   "An assumption that the distribution is log-normal is reasonable, as is an assumption of a difference of a factor of 10-50 between median and upper 95th percentile people, as indicated by the series of examples provided in Chapter 4. It is clear that the difference is significantly greater than a factor of 1, the current implicit assumption in cancer risk assessment. In the absence of further research leading to more accurate distributional values or chemical-specific information, the committee recommends that EPA adopt a default distribution or fixed adjustment value for use in cancer risk assessment. A factor of 25 would be a reasonable default value to assume as a ratio between the median and upper 95th percentile persons' cancer sensitivity for the low-dose linear case, as would be a default lognormal distribution. A factor of twenty-five could be interpreted as a factor of 10 for pharmacokinetic variability, and a factor of 2.5 for pharmacodynamic variability. For some chemicals, as in the 4-aminobiphenyl case study below, variability due to inter-individual PK differences can be greater. In a cancer process, with long latency and multiple determinants, PD variability could be considerably greater than the suggested default. PD differences would include the various degrees among people in DNA repair and misrepair, surveillance of mutated cells, and accumulation of additional mutations, and other factors involved in progression to malignancy." –As described in the Silver Book.

   "A common assumption for noncancer end points is an overall factor of 10 to account for inter-individual variability—3.2 or 4 uncertainty factor for PK differences and 3.2 or 2.5 for PD differences (EPA, 2002; IPCS, 2005). For genotoxic metabolically activated carcinogens, Hattis and Barlow (1996), considering activation, detoxification and DNA repair alone, found greater PK variability with individuals at the median and the 95th percentile differing by a factor of 10. The factor was a central estimate, some chemicals exhibited greater and others

lesser PK variability. In the 4-aminobiphenyl case discussed below, additional physiologic factors such as storage in the bladder contributed to human variability in PK elements. The suggested default of 25 will have the effect of increasing the population risk (average risk) relative to the median person's risk by a factor of 6.8: For a log-normal distribution, the mean to median ratio is equal to $\exp(\sigma^2/2)$. When the 95th percentile to median ratio is 25, σ is 1.96 [=ln(25)/1.645], and the mean exceeds the median by a factor of 6.8. If the risk to the median human were estimated to be 10^{-6}, and a population of one-million persons were exposed, the expected number of cases of cancer would be 6.8 rather than 1.0." –As described in the Silver Book.

"Thus under this new default, the value for the median person would remain as provided by the current approach to cancer risk assessment; for a default of a factor of 25, the average would be higher by a factor of 6.8. It would be important for the cancer risk assessment to express inter-individual variability by showing the median and average population risks, as well as the range of individual risks for risk-management consideration." –As described in the Silver Book.

3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

In the Silver Book, the 4-aminobiphenyl case study uses/assumes inter-individual variability with a range of 50 (ratio of 95th percentile to median person) to illustrate how variability may be incorporated into cancer dose-response modeling.

"It reflects the factor of roughly 20-30 between median and upper 95th percentile individual sensitivity in pharmacokinetics and a modest factor for variability factors pertinent to PD differences in carcinogenesis." –As described in the Silver Book.

"This approach to dose-response analysis begins, as do the other examples above, with the derivation of the human POD distribution. When derived from animal data, the human POD is based on the animal POD and distributions of adjustment factor, such as for interspecies differences and study duration less than a lifetime. Here, the POD is taken from a model fitted at a dose in the lower end of the observable response range, and does not use an ED_{50}. Risk at lower dose than this POD for the median person is estimated by linear extrapolation, that is, risk is assumed to decrease linearly with dose below the POD. However, as illustrated in Chapter 4 (Table 4-1), people exposed to the same dose will differ in risk. Estimates of the spectrum of individual risks at a given dose can be based on a distribution that describes inter-human variability. The individual dose-response relationships allow the calculation of the population dose-response curve. This approach to dose-response assessment is illustrated in Figure 5-17 and through the case study for 4-aminobiphenyl." –As described in the Silver Book.

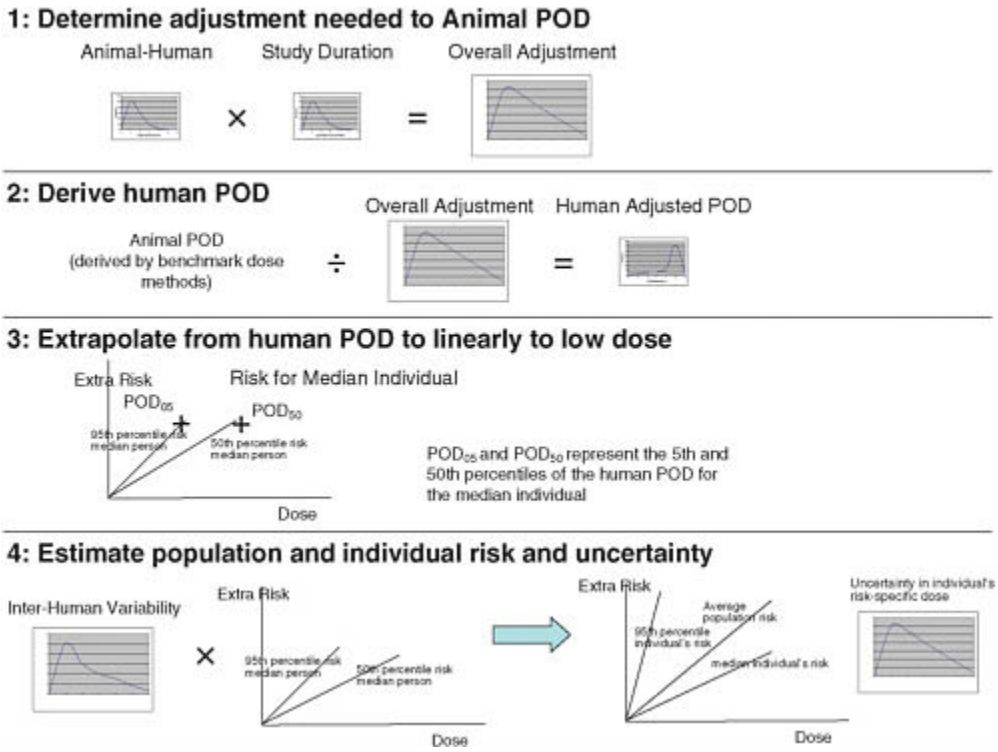

FIGURE 5-17 Steps to derive population and individual risk estimates, with uncertainty in estimates from animal data. Step 1 involves derivation of adjustment distribution to convert animal POD to human POD. Step 2 involves derivation of human POD from this distribution. Step 3 is linear extrapolation from POD to lower doses for median person. Lower bound on human POD is used to derive upper-bound risks for median person. Step 4 involves applying inter-individual variability distribution to estimate average risk to population and risks to individuals with different degrees of sensitivity, with uncertainty in estimates.

4. Proposed team to develop case study (desired, but optional)

References:

EPA (U.S. Environmental Protection Agency). 2002. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. December 2002 [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55365.

Hattis, D., and K. Barlow. 1996. Human interindividual variability in cancer risks - technical and management challenges. Hum. Ecol. Risk Assess. 2(1):194-220.

IPCS (International Programme for Chemical Safety). 2005. Guidance for the use of data in development of chemical-specific adjustment factors for interspecies differences and human variability. Pp. 25-48 in Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in

Dose/Concentration-Response Assessment. Harmonization Project Document No. 2. International Programme for Chemical Safety, World Health Organization, Geneva [online]. Available: http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf.

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1. **Please identify the issue/problem formulation that the proposed method aims to address (*e.g.*, Screening level assessment).**

   Evaluating the concept of how background or endogenous processes may be used in determining the potential for low-dose linearity of systemic toxicants. (Silver Book, Page 156-158)

   The evaluation will consist of a critical review of the methodology, evaluation of the assumptions and models, and discussion of whether the underlying biological processes do or do not support adopting such a default approach.

   If the default approach is determined to not be appropriate, then an alternative approach may be developed.

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   "Variability is expected to be much greater in the human population than in tester strains bred for use in the laboratory and exposed under controlled conditions, so it is important to reflect on potential human processes in reaching overall conclusions. However, animal studies can be more thorough in evaluating age-related and spontaneous toxicity in the control group than is typically possible in unexposed or reference human populations. Therefore, animal toxicity studies may provide important insights into the potential for low-dose linearity." – As described in the Silver Book.

3. **Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

   "A case in point is 1,4-dioxane. This solvent produces histopathologic changes in the liver's Ito cells termed hepatic spongiosis—an inflammatory lesion of the sinusoidal and endothelial cells that can be progressive and is believed to be involved in the response to nitrosamines and other hepatocarcinogens in rodents (Karbe and Kerlin, 2002; Bannasch, 2003). This end point is sensitive to 1,4-dioxane exposure (Yamazaki *et al*., 1994) and is an example of a noncancer end point. However, evidence of its involvement as a precursor lesion in hepatocarcinogenesis could lead to its evaluation with a different analytic framework (for example, conceptual model 3). As shown below, control males have a high incidence (24%), whereas this lesion

was not detected in the control and lowest-dose females. The sex-specific differences in background incidence of and sensitivity to liver disease mirror the pattern of hepatocarcinogenesis in rats and humans, with males more commonly affected than females (West *et al.*, 2006). – As described in the Silver Book.

As seen in Figure 5-15, the high background rate of the toxic end point in males is associated with a steeper dose-response curve at low dose in males than in females; this is consistent with the shape of the dose-response curve expected on the basis of the background rate of response. – As described in the Silver Book.

The potential for background processes to affect the shape of the dose-response curve for specific toxicants as observed in animal studies should be considered in building PD variability distributions in humans and in evaluating the possibility of low-dose linearity. In the case of the hepatic effect caused by 1,4-dioxane, prefibrotic and precirrhotic findings in the human population would be helpful in weighing the relevance of findings on animal vulnerability to that likely to occur in people. Diagnostic methods that can detect subtle liver damage in humans, such as ultrasonography and liver-function tests, may help in exploring background vulnerability to hepatotoxicants if developed further and applied to populations of healthy people (Hsiao *et al.*, 2004; Maroni and Fanetti, 2006). Existing underlying conditions and their causes could be considered in the context of potential mechanisms of 1,4-dioxane toxicity to evaluate whether the dose-response relationship should be treated as linear or nonlinear at low doses. – As described in the Silver Book.

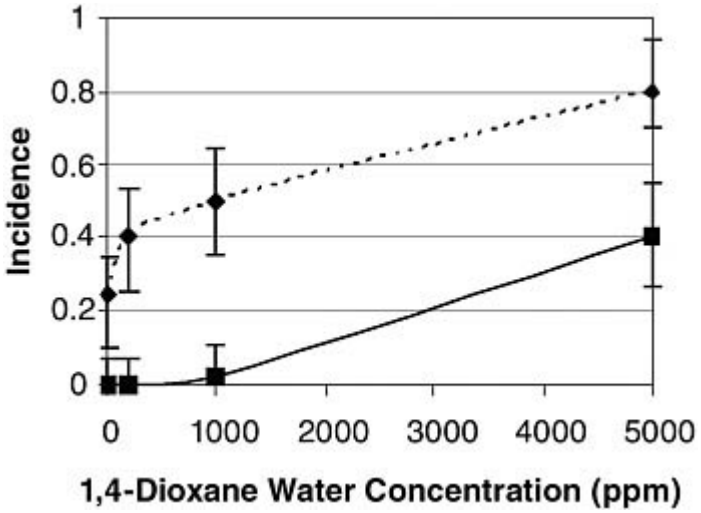

FIGURE 5-15 Dose-response relationship for liver spongiosis in 1,4-dioxane-exposed rats. Males: diamonds; females: squares. Bars indicate the 95% confidence intervals.
Source: Adapted from Yamazaki *et al.*, 1994.

4. Proposed team to develop case study (desired, but optional)

References

Bannasch, P. 2003. Comments on 'R. Karbe and R. L. Kerlin. (2002). Cystic Degeneration/Spongiosis Hepatis [Toxicol. Pathol. 30(2):216-227].' Toxicol. Pathol. 31(5):566-570.

Hsiao, T.J., J.D. Wang, P.M. Yang, P.C. Yang, and T.J. Cheng. 2004. Liver fibrosis in asymptomatic polyvinyl chloride workers. J. Occup. Environ. Med. 46(9):962-966.

Karbe, R., and R.L. Kerlin. 2002. Cystic degeneration/Spongiosis hepatis in rats. Toxicol. Pathol. 30(2):216-227.

Maroni, M., and A.C. Fanetti. 2006. Liver function assessment in workers exposed to vinyl chloride. Int. Arch. Occup. Environ. Health 79(1):57-65.

West, J., H. Wood, R.F. Logan, M. Quinn, and G.P. Aithal. 2006. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971-2001. Br. J. Cancer 94(11):1751-1758.

Yamazaki, K, H. Ohno, M. Asakura, A. Narumi, H. Ohbayashi, H. Fujita, M. Ohnishi, T. Katagiri, H. Senoh, K. Yamanouchi, E. Nakayama, S. Yamamoto, T. Noguchi, K. Nagano M. Enomoto, and H. Sakabe. 1994. Two-year toxicological and carcinogenesis studies of 1, 4-dioxane in F344 rats and BDF1 mice: Drinking studies. Pp. 193-198 in Proceedings of the Second Asia-Pacific Symposium on Environmental and Occupational Health, 22-24 July, 1993, Kobe, Japan, K. Sumino, and S. Sato, eds. Kobe: International Center for Medical Research Kobe, University School of Medicine.

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   A case study of ethanol. An IARC known human carcinogen, a human teratogen (fetal alcohol syndrome), a chronic liver toxicant (alcoholic cirrhosis), and an acute neurotoxicant.

   There are well known human polymorphisms in alcohol metabolism: individual (and ethnic) alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), and cytochrome P-4502E1(CYPIIE1). A deficiency of the ALDH2 isozyme in certain individuals and ethnic groups is responsible for the flushing symptoms as well as other vasomotor symptoms caused by a higher acetaldehyde level after alcohol consumption. A low proportion of ALDH2

deficiency (ALDH2*2 allele frequency) was found in alcoholics compared with healthy controls, and polymorphism of ALDH2 and/or CYP2E1 may be associated with the susceptibility to alcohol-induced liver injury.

There are numerous sources of ethanol exposures in addition to the consumption of alcoholic beverages. These include exposures from fruits, breads, and other food products. One exposure that may be very illustrative in helping to evaluate the question of whether the biological processes associated with effects of low levels of exposures of a systemic toxicant are best represented by a linear dose response is the exposure of children to quantifiable levels of ethanol in fruit juices. For example, ethanol content in apple juice and grape juice may be "not more than 5 gr/kg juice," and in orange juice "not more than 3 gr/kg juice."

http://siweb.dss.go.th/standard/Fulltext/codex/CXS_048E.pdf
http://siweb.dss.go.th/standard/Fulltext/codex/CXS_082E.pdf
http://siweb.dss.go.th/standard/Fulltext/codex/CXS_045E.pdf

On a weight basis, this corresponds to 0.5% and 0.3%, respectively, for apple and grape juice, and for orange juice. For comparative purposes, alcohol content in beer ranges from 4 to 6 %; and in wine from 8 to 20%; thus the average ethanol content of beer on a weight basis would be ~50 g/kg beer (5% = 50 g/kg beer).

http://www.alcoholcontents.com/wine/wine.htm

4. Proposed team to develop case study (desired, but optional)

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:

Harvey Clewell
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hclewell@thehamner.org

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

An assessment is needed for a high-production volume chemical, for which population exposure is substantial, both in consumer products and as a result of legacy site contamination.

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

Due to the high potential for exposure and high economic importance of the chemical, a high degree of precision is needed for the dose-response assessment. A biologically based dose-response (BBDR) model provides the needed precision, by incorporating biological data on the mode of action into the mathematical description of the dose-response for the chemical of interest. Both the structure and the parameters in the model should, to the extent possible, be derived from the mode-of-action information available for that chemical. In the case of a carcinogenic effect, such a BBDR model would take the tissue dosimetry from a PBPK model as input and predict the resulting tumor incidence over time in both rodents and humans, in place of empirical (e.g., benchmark) dose-response modeling. It is important to note that, as defined by the USEPA cancer guidelines, a BBDR model cannot, in the end, be essentially empirical; that is, it cannot merely represent a statistical fit to bioassay tumor incidence data, no matter how sophisticated the biological constructs in the model. Instead, the parameters in the model must have direct biological correspondence (mutation rates, cell division rates, etc.), similar to the requirements for the parameters in the PBPK model, and must have been determined on the basis of experiments apart from the animal bioassays themselves.

Clonal growth (CG) models have been used since the 1970's to study how cell replication and mutation influence tumor incidence (Moolgavkar and Venzon, 1979; Moolgavkar and Knudson, 1981; Moolgavkar, 1986; Moolgavkar et al., 1988). The most commonly used CG model has 2 stages and is not meant to represent the detailed biochemical mechanism of most cancers (though the original development of the 2-stage CG model was motivated by data on childhood retinoblastoma, which may well be a 2-stage cancer). More elaborate and mechanistically accurate CG models have been

developed when the supporting data were adequate (e.g., a 4-stage model for colorectal carcinoma was described by Luebeck and Moolgavkar [2002]). On the other hand, simplified deterministic approximations to the fully stochastic model have also been described (Clewell et al., 1995; Hoogenveen et al. 1999).

The 2-stage CG model (Figure 1) is best thought of as a biologically motivated model of cancer in that it describes a multistage process and allows for straightforward incorporation of data on cellular proliferation and mutation. The implications for tumor dose-response of separate dose-responses for cellular proliferation and mutation can be studied with the 2-stage model.

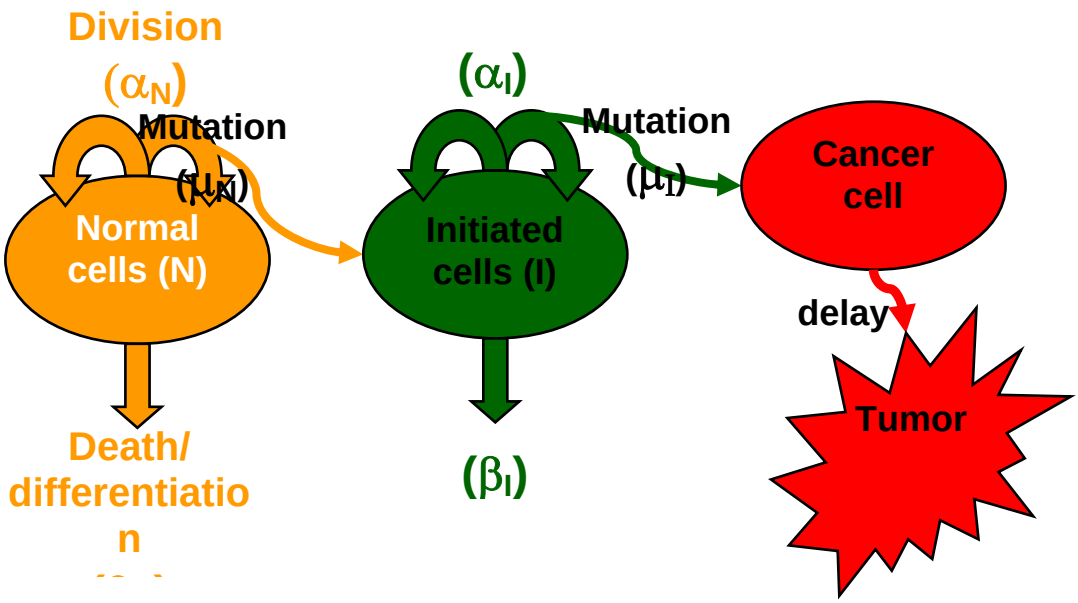

Figure 1: Diagram of a 2-Stage Clonal Growth Cancer Model.

Equations for deterministic 2-stage clonal growth model (Hoogenveen et al. 1999):

$$\frac{dN}{dt} = N(\alpha_N - \beta_N) \qquad \text{Initial condition} = N_0$$

$$\frac{dI}{dt} = I(\alpha_I - \beta_I) + N\alpha_N\mu_N$$

$$\frac{dI}{dt} = I(\alpha_I - \beta_I) + N\alpha_N\mu_N - I\alpha_I\mu_I\left(1 + \frac{I\alpha_I}{N\alpha_N\mu_N}\right)$$

$$p(tumor) = 1 - e^{-\int I\alpha_I\mu_I}$$

N = normal cell number (#cells/cm^2)
α_N = cell division rate of normal cells (h^{-1})
β_N = cell death rate of normal cells (h^{-1})
I = Intermediate cell number (#cells/cm^2)
α_I= cell division rate of intermediate cells (h^{-1})
β_I = cell death rate of intermediate cells (h^{-1})
μ_N = mutational rate (from normal cells to intermediate cells)
μ_I = mutational rate (from intermediate cells to tumor cells)

References:

Clewell HJ, Quinn D, Andersen ME, Conolly RB. (1995). A straightforward approximation to the exact solution of the two stage clonal growth model of cancer. Risk Anal 15:467-473.

Hoogenveen, R.T., Clewell, H.J., Andersen, M.E., Slob, W. (1999). An alternative exact solution to the two-stage clonal growth model of cancer. Risk Analysis 19, 9-14.

Luebeck, E.G., and Moolgavkar, S.H. (2002). Multistage carcinogenesis and the incidence of colorectal carcinoma. P.N.A.S. 99, 15095-15100.

Moolgavkar, S. H. (1986). Carcinogenesis modeling: From molecular biology to epidemiology. Annu. Rev. Public Health 7, 151-169.

Moolgavkar, S. H. and Venzon, D. J. (1979). Two-event models for carcinogenesis: Incidence curves for childhood and adult tumors. Math. Biosci. 47, 55-77.

Moolgavkar, S. H. and Knudson, A. G. Jr. (1981). Mutation and cancer: A model for human carcinogenesis. J. Natl. Cancer Inst. 66, 1037-1052.

Moolgavkar, S. H., Dewanjii, A., and Venzon, D. J. (1988). A stochastic two-stage model for cancer risk assessment. I. The hazard function and probability of tumor. Risk Anal. 8, 383-392.

3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

Formaldehyde biologically-based dose-response model:

Conolly and colleagues (Conolly et al. 1992) proposed that the mode of action for the carcinogenicity of formaldehyde was increased fixation of background mutations by cytotoxicity-driven cell proliferation, and described an approach using a 2-stage clonal growth model to evaluate the dose-response for this process. The resulting 2-stage clonal growth model for formaldehyde carcinogenicity in the rat and human (Conolly et al.

2003, 2004) predicted a low-dose J-shaped dose response for tumors when a J-shaped dose-response for regenerative proliferation and a low-dose-linear dose-response for direct mutagenicity were used as model inputs. The conclusions of Conolly et al. (2004) were that "the human implications of the rat squamous cell carcinoma (SCC) data indicates that (1) cancer risks associated with inhaled formaldehyde are de minimis (10-6 or less) at relevant human exposure levels and (2) protection from the non-cancer effects of formaldehyde should be sufficient to protect from its potential carcinogenic effects"

References:

Conolly RB, Morgan KT, Andersen ME, Monticello TM, Clewell HJ. (1992). A biologically-based risk assessment strategy for inhaled formaldehyde. Comments Toxicol 4:269 293.

Conolly, R.B., Kimbell, J.S., Janszen, D., Schlosser, P.M., Kalisak, D., Preston, J., and Miller, F.J. (2003). Biologically motivated computational modeling of formaldehyde carcinogenicity in the F344 rat. Toxicol. Sci. 75, 432-447.

Conolly, R.B., Kimbell, J.S., Janszen, D., Schlosser, P.M., Kalisak, D., Preston, J., and Miller, F.J. (2004). Human respiratory tract cancer risks of inhaled formaldehyde: dose-response predictions derived from biologically-motivated computational modeling of a combined rodent and human dataset. Toxicol. Sci. 82, 279-296.

4. Proposed team to develop case study (desired, but optional)

Harvey Clewell, Mel Andersen, Rory Conolly, Bruce Allen

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Your Name, affiliation, and e-mail:
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1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

   Establish screening-level health protective exposure limits for a chemical using minimal data, such as structure or class information, that is applicable to new chemicals or chemicals that may have emerging health concerns but lack a robust data set.

2. **Please describe the proposed method (1-3 pages). Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

This method will use a hybrid approach, based on the available toxicity data for the chemical or class as well as quantitative toxicity data from qualitatively-identified analogues. (The full assessment also includes screening-level evaluation of ecotoxicity and exposure, but this proposal focuses on human health hazard screening and concern dose prediction.)

For this screening assessment, a broad search is conducted for relevant data on the chemical of interest or chemical class. In many cases, data on the chemical are very limited, and so toxicology data on structural analogues and degradation products, if applicable, as well as QSAR predictions, are used. Professional judgment is used to identify preferred analogues, focusing on key reactive structural groups that are likely to influence toxicity. Decision criteria have already been developed for identifying health concerns and for selecting analogues. Using data available for the analogues, effect levels are identified, and are combined with estimates of general population, consumer, occupational and aquatic exposure to develop risk assessments for applicable scenarios and targets. In addition to determining potential risk from identified potential exposures, this methodology could be used to estimate predicted exposure levels at which risk may be indicated.

Analogues are identified from a suite of sources, and evaluated based on structural similarity, the presence and relationship of key functional groups, and similarity of key physical properties. Selected analogues should be similar in size to the test compound, and should not contain additional functionality. Once analogues have been identified, a search is conducted for toxicity information; available toxicity data on the chemical of

interest and the analogue (e.g., LD_{50}) should be consistent. This is an iterative approach, and different analogues may be used for different endpoints, depending on the available data. Degradation products resulting from hydrolysis, as well as likely metabolites, may also be considered. Based on the toxicity data on the chemical of concern and its analogues, as well as information on chemical/physical properties and professional judgment, a level of concern (low, moderate, or high) and an effect level (mg/kg-day) are assigned for systemic, reproductive, developmental, immunotoxicity, and neurotoxicity effects. If appropriate, these ratings take into account the impact of chemical properties on toxicity, such as the low bioavailability of polymers and the low concern for inhalation exposure for chemicals with low vapor pressure.

In order to complete a quantitative risk assessment, exposure scenarios are developed which reflect the potential uses of the chemical or the chemical class, and the group(s) to which exposure may occur (occupational, general population, consumer, children, etc.). The release and exposure profile includes assessment of potential exposure dose rates to humans through occupational (worker) exposure and general population (downstream industrial release, consumer use, disposal, etc.) and to the environment (downstream industrial release, disposal, etc.).

The estimated exposure data are then combined with the hazard profile to give an overall risk profile. Risk to human health is established by comparison of any predicted human/mammalian toxicity effect levels (typically LOAELs or NOAELs) with the estimated human exposure dose rates (occupational and general population) to give a margin of exposure (MOE). The magnitude of the MOE determines if the potential for risk to human health exists. For example, in the context of the Sustainable Futures program, a margin of exposure that is considered to indicate negligible risk when using a LOAEL to exposure dose rate comparison is 1000, while it is 100 for a comparison using a NOAEL.

This stepwise risk assessment paradigm allows for examination of all factors that may contribute to potential risk. The approach constitutes a rapid screening method to characterize chemicals and distinguish those that have the potential for risk from those that do not, therefore identifying the chemicals or exposure routes which may benefit from closer examination or which may require mitigation efforts. This is a flexible methodology which allows the targeting of particular risk areas, such as risks to children, by adjusting individual parameters in the exposure or other calculations. This overall approach has been applied to dozens of chemicals by the team, with results which have been used for various purposes, such as MSDS hazard statement development, PMN submissions, and other chemical assessment tasks. Since the screening assessments are consistently based on worst case scenario assumptions, it is unlikely that risk potential will be understated.

3. **Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

The case study proposed uses the Sustainable Futures ™ Pollution Prevention (P2) assessment paradigm, which has been developed for the hazard/risk assessment of new or existing chemicals with limited data. The theoretical example chemical is a branched C16-C18 alpha-olefin sulfonate, a type of surfactant typically used as a dispersant or component in cleaning products. The first step in a three-part approach includes developing a hazard assessment summary, which begins with the complete evaluation of the chemical's hazard potential, using chemical/physical properties, QSAR analysis for estimating physical/chemical properties and ecotox characteristics including persistence and bioaccumulation. The hazard assessment is completed using toxicity data on the chemical, its analogues, and for its chemical class to determine the potential hazard levels and probable toxicity effects on organs and systems.

Next, in order to determine screening level, health-protective risk assessment exposure limits, some exposure and release scenarios must be applied. The QSAR model ChemSTEER is used to determine the magnitude of releases to the environment for manufacturing, processing, and use scenarios, as well as rates of occupational exposure. Estimated releases are then modeled using E-FAST, which predicts exposure rates to consumers and the general population from the releases.

Finally, margins of exposure are calculated utilizing common toxicological principles to extrapolate from mammalian data and other factors, which may then be used to estimate the health protective levels (levels of no concern).

4. Proposed team to develop case study

Elizabeth Becker, Ph. D., Manager, Technical Services, CERM (Team Leader)

Peter Ranslow, Ph. D., Director of Risk Assessments, CERM

Interpretive assistance from researcher or toxicologist from *TERA*, as needed.

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail: ACC ARASP Center

1. Please identify the issue/problem formulation that the proposed method aims to address (*e.g.*, Screening level assessment).

Evaluating the assumption that small chemical exposures in the presence of existing disease processes and other endogenous and exogenous exposures can have linear dose-response relationships at low doses. (Silver Book, Page 158-160)

The evaluation will consist of a critical review of the methodology, evaluation of the assumptions and models, and discussion of whether the underlying biological processes do or do not support adopting a default approach such as linear extrapolation from the POD (benchmark dose) down to low doses.

If the default approach is determined to not be appropriate, then an alternative approach may be developed.

2. Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).

Default Modeling Approach for Conceptual Model 1: Linear Extrapolation for Phosgene

As described in the Silver Book:

"As described above, small chemical exposures in the presence of existing disease processes and other endogenous and exogenous exposures can have linear dose-response relationships at low doses. Thus, a simple methodologic default to address conceptual model 1 compounds is linear extrapolation from the POD, such as a benchmark dose, down to low doses. Greater information on MOA and chemical interactions with background disease processes and similarly acting chemicals may allow different low-dose extrapolations. For example, the slope of the line at the POD or another particular dose could be adjusted, as described below for conceptual model 3.

"Linear low-dose extrapolation for a noncancer end point is illustrated with the case example of phosgene. This reactive respiratory toxicant damages the airways at high doses, and dose-response studies in rats exposed for 12 weeks report effects of inflammation and fibrosis of the bronchiolar region (Kodavanti *et al.*, 1997; EPA, 2005). The BMD_{10} for this phosgene effect in rats is 170 $\mu g/m^3$ as a human equivalent concentration (HEC). The lower 95% confidence bound—the $BMDL_{10}$—is 30 $\mu g/m^3$. To this an adjustment is made because the study is subchronic rather chronic, and chronic exposure is of interest in calculating an alternative RfD.

"In considering how this risk may be manifested in human populations, the background incidence of asthma—about 6% in children (CDC, 2007)—is relevant. Asthmatics experience inflammation, fibrosis, and airway remodeling in response to environmental allergens and irritants, and so constitute a large population potentially vulnerable to phosgene. In addition there are numerous medical conditions (for example, infection, environmental exposures, and pharmaceuticals) that lead to the lung inflammation and fibrosis that would potentially be worsened by phosgene exposure. Thus, there is a potential for background additivity that is consistent with conceptual model 1 and linear extrapolation to low dose. Further analysis of cell types and disease processes involved in phosgene toxicity and the other medical conditions may lead one to discover otherwise, but absent more definitive information indicating implausibility, background additivity would be assumed.

"Box 5-2 shows that a linear extrapolation from the BMD derived by EPA would yield a risk-specific dose (median estimate) of 0.0085 $\mu g/m^3$ phosgene exposure. Theoretically, exposure at this dose is predicted to contribute to inflammation and fibrosis in 1 in 10^5 of exposed individuals. The phosgene RfC of 0.3 $\mu g/m^3$, set by EPA with a 100-fold cumulative uncertainty factor, corresponds to a theoretical risk that 1 in 3,000 (median estimate) individuals could be affected, on the basis of linear extrapolation. Implicit in the extrapolation are the assumptions that a 10-fold reduction in exposure will result in a 10-fold reduction in risk and that the $BMDL_{10}$ in terms of the HEC is the human 10% effect dose. This approach could be refined to explore the variability between individuals that is possible because of pharmacokinetics, the incidence and distribution of relevant respiratory health conditions, and many other factors, and to explore issues regarding species dose-effect concordance for phosgene. Here, as for conceptual model 3, an important issue is whether dose effectiveness is the same at high doses and low doses. Extrapolation methods for addressing that are discussed in the section below on the mathematical framework for conceptual model 3."

3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

Quote from Page 159 of Silver Book:

Conceptual Model 1: Default Linear Low-Dose Extrapolation for Phosgene

1. Assume uncertainty in all parameters can be characterized by a lognormal distribution, with standard deviation represented by σ.
2. BMD_{10} (human equivalent concentration) = 170 $\mu g/m^3$, with 95%-tile lower bound 30 $\mu g/m^3$ variability in animal BMD, with a difference between lower 95% bound and median of 5.7-fold (because 5.7=170/30):

$$\sigma_{\text{Animal BMD}} = \log(5.7)/1.645 = 0.46$$

(Division by the 95% confidence bound is 1.645 standard deviations from the median in the standard normal distribution.)

3. The human equivalent concentration accounts for cross-species differerence in pharmacokinetics but not pharmacodynamics.

Assume, as in Hattis et al. 2002, that $\sigma_{\log A \rightarrow H} = 0.42$

4. Median human POD:

Adjust for subchronic to chronic study length, as in Hattis et al. 2002, by a factor of 2:

$$170\ \mu g/m^3 \div 2 = 85\ \mu g/m^3$$

Assume the uncertainty ($\sigma_{logSC\rightarrow C}^2$) in the adjustment, as in Hattis *et al*., 2002:

$$\sigma_{logSC\rightarrow C} = \log[2.17] = 0.34$$

5. Uncertainty in the human POD ($\sigma_{logHuman\ POD}$):

$$\sigma^2_{logHuman\ POD} = \sigma^2_{logAnimal\ BMD} + \sigma^2_{logA\rightarrow H} + \sigma^2_{logSC\rightarrow C}$$
$$\sigma^2_{Human\ POD} = 0.46^2 + 0.42^2 + 0.34^2 = 0.71^2$$

6. Lower 95% confidence bound on Human POD = (median human POD)/$10^{[(1.645)(\sigma logHuman\ POD)]}$ = $85/10^{[(1.645)(0.71)]}$ = 85/14.7 = 5.8 $\mu g/m^3$

7. Linear extrapolation to risk-specific dose - inflammation of 1 in 10^5 people would be affected:
   risk-specific dose = $10^{-5} \times (85/0.1)$ = 0.0085 $\mu g/m^3$, with lower bound 0.00058 $\mu g/m^3$

8. Estimate risk at different doses: for example, at 0.01 $\mu g/m^3$, three people in 10^5 (median estimate) would be affected.

4. Proposed team to develop case study (desired, but optional)

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References

CDC (Centers for Disease Control and Prevention). 2007. Asthma: Asthma's Impact on Children and Adolescents. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Washington, DC [online]. Available: http://www.cdc.gov/asthma/children.htm.

EPA (U.S. Environmental Protection Agency). 2005d. Toxicological Review of Phosgene (CAS 75-44-5) In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-06/001. U.S. Environmental Protection Agency, Washington, DC. December 2005 [online]. Available: http://www.epa.gov/iris/toxreviews/0487-tr.pdf.

Hattis, D., S. Baird, and R. Goble. 2002. A straw man proposal for a quantitative definition of the RfD. Drug Chem. Toxicol. 25(4):403-436.

Kodavanti, U.P., D.L. Costa, S.N. Giri, B. Starcher, and G.E. Hatch. 1997. Pulmonary structural and extracellular matrix alterations in Fischer F344 rats following subchronic phosgene exposure. Fundam. Appl. Toxicol. 37(1):54-63.

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:

Ted Simon
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1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

An assessment is needed for 2,3,7,8-tetrachlorodibenzodioxin (TCDD), a ubiquitous chemical present in both the food supply and environmental media. The entire world's population is exposed to this chemical, although some groups have experienced greater historical exposure. Although well-conducted animal bioassays are available, they provide little information because humans respond to this chemical very differently than laboratory animals.

The Silverbook describes three conceptual models for individual/population dose response; these three models represent assumptions about mode of action, background exposures and underlying disease processes. A data-rich chemical such as TCDD would permit exploration of all three models as a way to understand the consequences of choosing one of the conceptual models over the other two.

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

It is well known that TCDD exerts its effects by activation of the aryl hydrocarbon receptor (AHR). Expressing biochemical measures such as mRNA expression or enzyme activity in terms of fractional AHR expression permits mapping of various toxic effects observed at specific AHR activation levels as a tool for intra- and interspecies extrapolation or for in vitro to in vivo extrapolation. Hence, this toxicity mapping is a function-based dose metric rather than a tissue concentration dose metric and represents another tool for the extrapolations/adjustments used in risk assessment as described in chapter 5 of the Silverbook.

Knowledge of mode of action provides the basis for biologically-based dose-response (BBDR) modeling and the use of such models increases biological plausibility and diminishes the need to use default assumptions. TCDD is one of the most intensively studied chemicals, both in terms of epidemiology and basic biology, and TCDD likely exceeds the requirements of the knowledge base to support using a BBDR rather than a purely statistical model for risk assessment. In addition, because dioxin is ubiquitous in the environment and humans receive low-level exposure from the food supply, the Silverbook recommendations to consider background processes and exposures can be explored in detail for TCDD.

Because the AHR plays a role in normal development and maintenance of homeostasis, it will be important to distinguish its normal function from its role in toxicity. The extensive knowledge of AHR biology will permit the exploration of the role of background exposures to AHR ligands, underlying disease processes, and multiple modes of action operative at different dose ranges.

Data exist to support interspecies toxicodynamic extrapolation of AHR responses to TCDD and a toxicokinetic model is available for toxicokinetic extrapolation.

3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

BBDR for TCDD

Simon (2009) and Simon et al (unpublished) applied the Silverbook method to TCDD and determined that the key event in the mode of action is dysregulation of normal AHR function. From caffeine metabolism studies, AHR activation in humans from dioxin-like chemicals can be expressed as a fractional amount using the Hill dose-response model. The baseline activation level appears to be about 8% (Lambert et al., 2006; Abraham et al., 2002). Using studies of both humans and human AHR "knock-in" mice, the threshold for AHR dysregulation appears to be about 30%. This threshold would correspond to a serum concentration of 1650 ppt lipid. Accounting for both TK and TD variability in humans, the 90% confidence interval of the corresponding dose would be 0.5 to 53 ng/kg/d with a central value of 6 ng/kg/d. Hence, because of the necessity for normal AHR function in humans and the appearance of a threshold for dysregulation, conceptual model #2 would be implemented and the value of 0.5 ng/kg/d or 500 pg/kg/d would selected as the reference dose (RfD).

References:

Abraham, K., Geusau, A., Tosun, Y., Helge, H., Bauer, S. and Brockmoller, J. (2002). Severe 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication: insights into the measurement of hepatic cytochrome P450 1A2 induction. *Clin.Pharmacol.Ther.* **72**, 163-174.

Lambert, G. H., Needham, L. L., Turner, W., Lai, T. J., Patterson, D. G., Jr. and Guo, Y. L. (2006). Induced CYP1A2 activity as a phenotypic biomarker in humans highly exposed to certain PCBs/PCDFs. *Environ Sci Technol* **40**, 6176-6180.

Simon T (2009) Cancer Potency Estimates for 2,3,7,8-TCDD developed from the National Toxicology Program Bioassay Results, *The Toxicologist*, Program **#EA1-2251**

Simon T, Budinsky RA, Rowlands JC (2009) Application of the National Research Council Method for Dose Response Assessment to 2,3,7,8-Tetrachlorodibenzo(p)Dioxin, unpublished

4. Proposed team to develop case study (desired, but optional)

Ted Simon, Bob Budinsky, J. Craig Rowlands

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:
Bruce Allen, Bruce Allen Consulting, bruce_allen@verizon.net

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

   Extending the dose-response curve down to environmentally- or occupationally-relevant exposure levels

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

Identify a series of events in the pathway for the endpoint of interest, for which dose-response data exist. Normalize as appropriate to facilitate the combination of observations that may have been reported in different formats (e.g., as percent of control from one study but with mean values in another study). Use a series of linked "cause-effect" functions, fit by maximization of the likelihoods associated with the observed data and the models linking successive steps. Thus, for example, the second step in the progression is described as a function of the first step, and the third step is described as a function of the second step (thus including the relationship to the first step). Continuous endpoints can be linked to the previous term by such equations as the power model, and equations such as the logistic model can be used to predict the response for quantal endpoints.

3. **Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

Titanium dioxide is hypothesized to cause lung tumors via an inflammatory MOA. The appropriate dose metric is surface area of particles per gram of lung tissue. The figures show the proposed succession of steps, and the linkages between the successive steps, with the ultimate result of linking an internal dose metric (lung burden) through precursor changes (inflammatory cell changes, etc.) to the ultimate toxic effect.

Figure 1. TiO_2 Tumor Progression

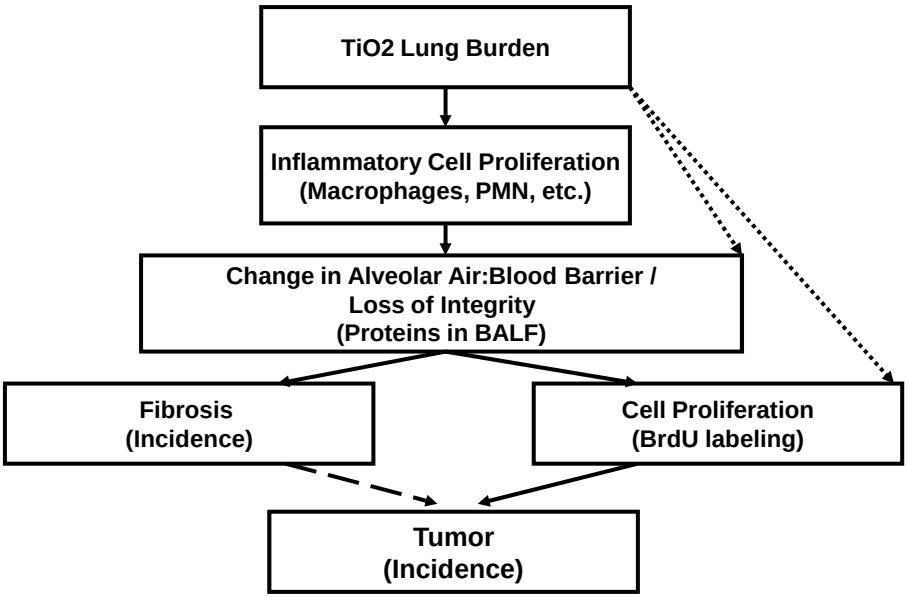


Figure 3. PMN vs Lung Burden

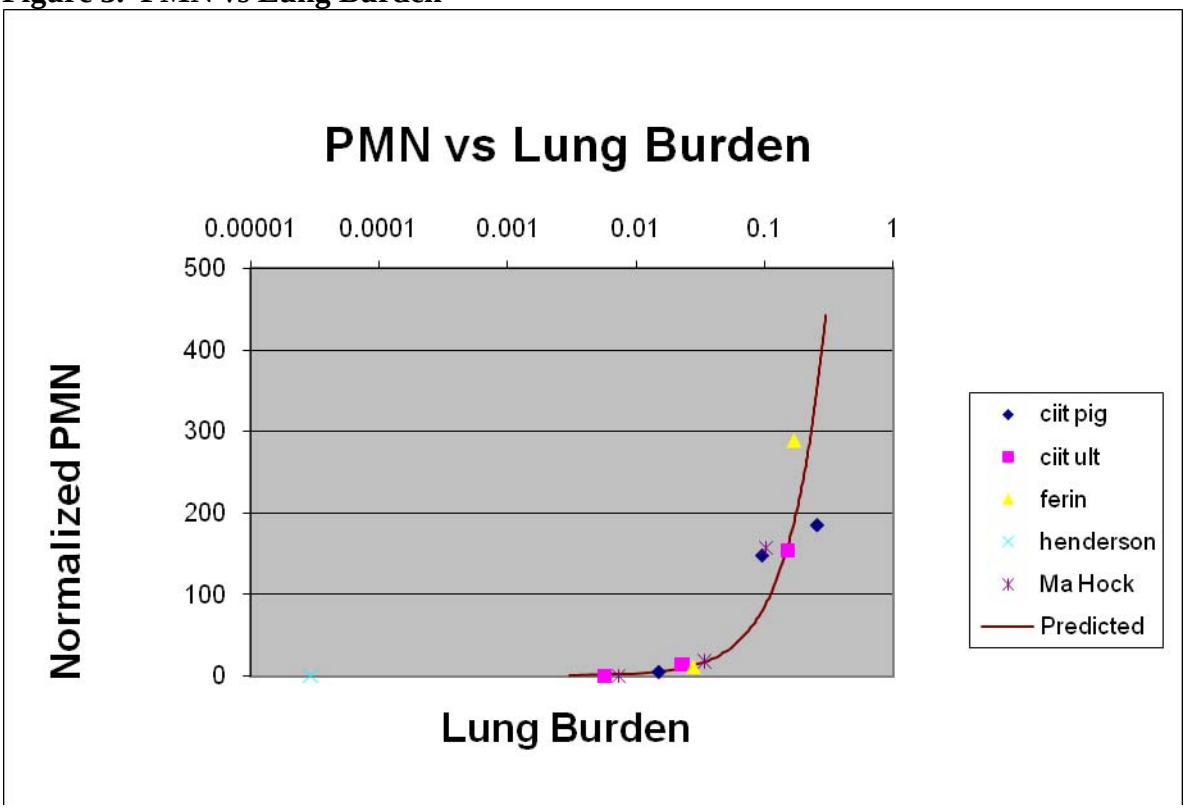


Figure 4. LDH vs Lung Burden

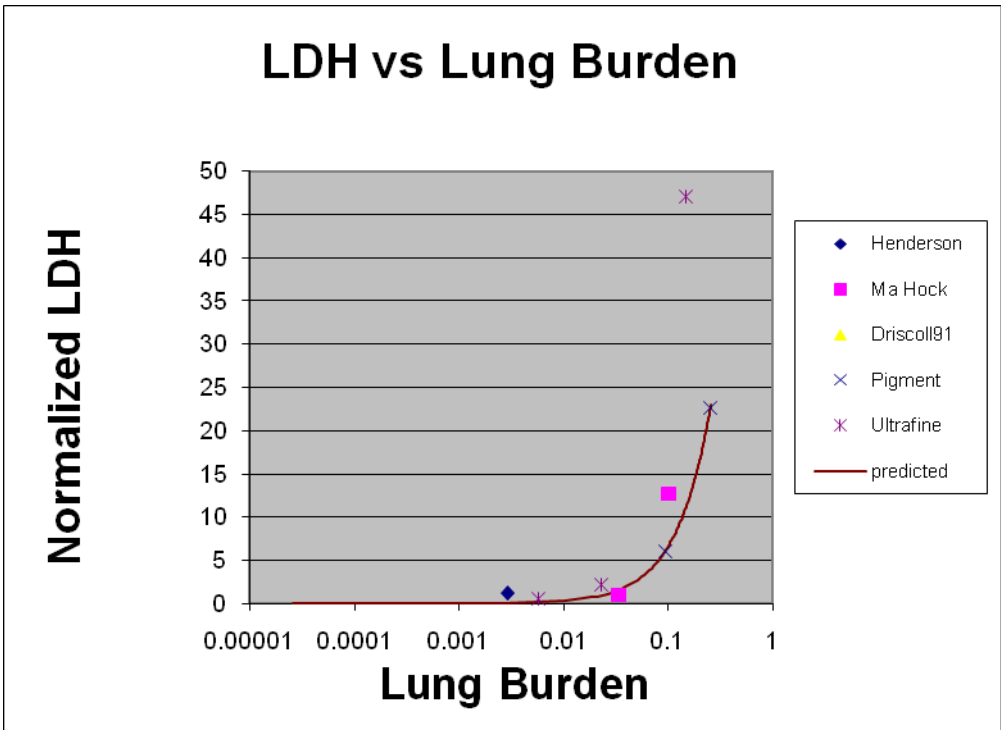


Figure 5. Alveolar Cell BrdU Index vs Lung Burden

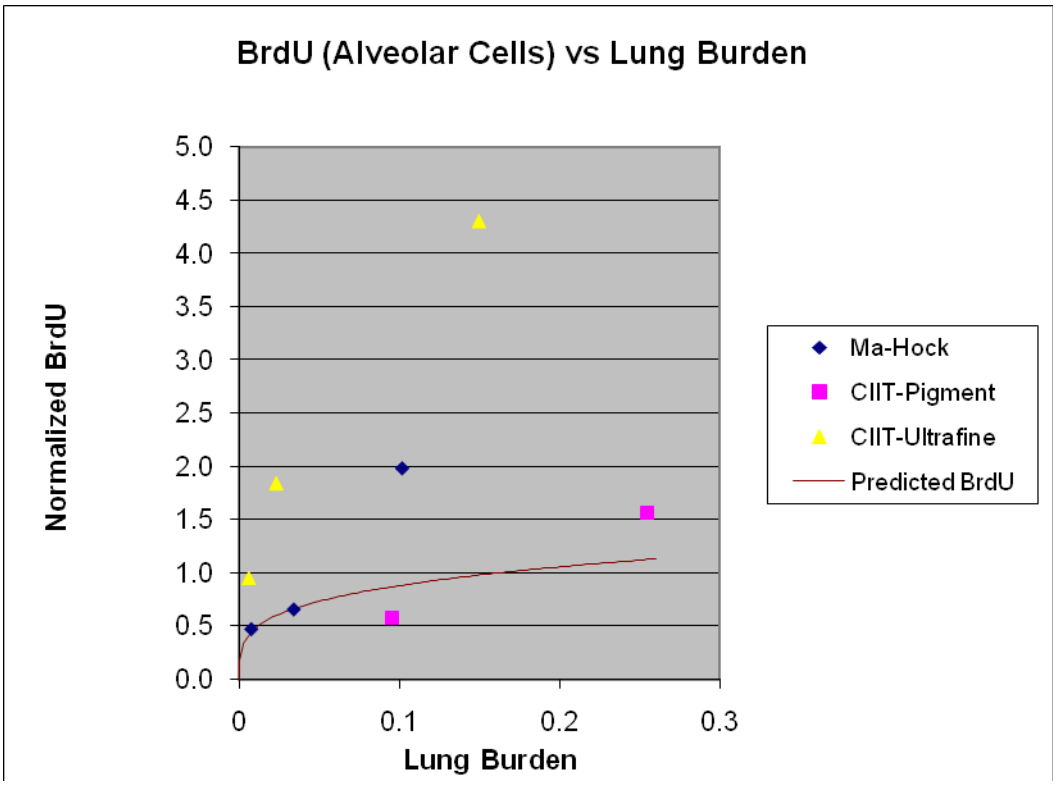


Figure 6. Fibrosis vs Lung Burden

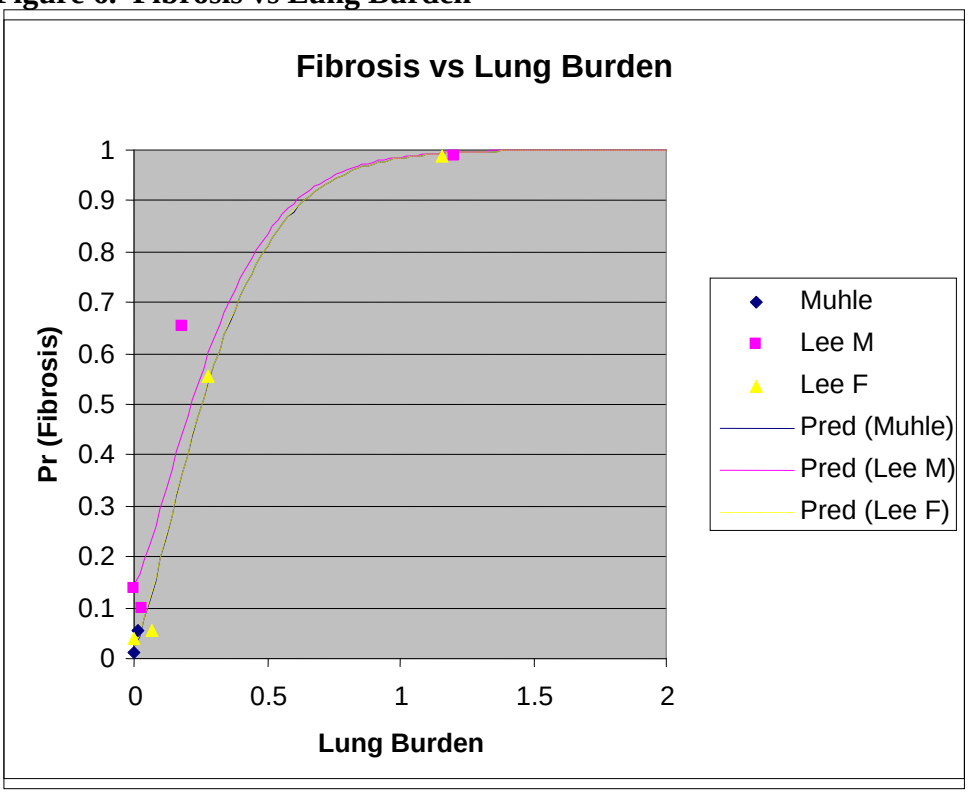


Figure 7. Lung Tumor vs Lung Burden

4. Proposed team to develop case study (desired, but optional)

Bruce Allen
Lynne Haber
Tba: NIOSH

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:

tbd

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

Considering uncertainty in cancer dose-response assessment.

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

A critical question related to evaluating cancer risk is the evaluation of uncertainty. There are currently no means of estimating the uncertainty
associated with default cancer methods, and therefore for comparing that uncertainty with that associated with conducting biologically-based dose-response (BBDR) modeling. BBDR incorporates biological mechanism and data for key intermediate events (between dose and penultimate response). A key question is the relative impact of model uncertainty and parameter uncertainty in a BBDR model, vs. the uncertainty associated with using default programs. Crump et al. (2008) conducted an extensive sensitivity analysis of the BBDR-based cancer assessment for formaldehyde of Conolly et al. (2004), concluding that a very high level of uncertainty exists, suggesting that estimates could plausibly be 10,000 times higher than that which Conolly et al. considered to be an upper bound. An analysis of the kind employed by Crump et al. to the BBDR-based formaldehyde assessment has never been applied to the default method, so we cannot say if an uncertainty level of 104 is truly large or modest by comparison.

The solution would be to develop a method or framework for conducting comparable uncertainty analyses on both default/statistical-modeling methods and BBDR-based methods.

Crump KS, Chen C, Fox JF, Van Landingham C, Subramaniam R. 2008.
Sensitivity analysis of biologically motivated model for formaldehyde-induced respiratory cancer in humans. Ann Occup Hyg. 52 (6):481-95.

Conolly RB, Kimbell JS, Janszen D, Schlosser PM, Kalisak D, Preston J, Miller FJ. 2004.
Human respiratory tract cancer risks of inhaled
formaldehyde: dose-response predictions derived from biologically-motivated computational modeling of a combined rodent and human dataset. Toxicol Sci. 82(1):279-96.

3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

tbd

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:
Michael Dourson
Toxicology Excellence for Risk Assessment (*TERA*)
dourson@tera.org

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

   For the purposes of conducting a cost-benefit analysis, estimate the probability of harm in a sensitive subgroup at various doses above the Reference Dose (RfD) or Reference Concentration (RfC).

2. **Please describe the proposed method (1-3 pages). Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   This method is a straightforward application of that developed by Swartout et al. (1998),[1] and can be adapted as needed with the receipt of additional data on individual uncertainty factors. For the purposes of this case study, however, only the published uncertainty factor distributions of Swartout et al. (1998) will be considered. The resulting probabilities do not reflect a body count, since the incoming data are not of this type. Rather, the probabilities represent a conservative estimate of the risk of the critical effect occurring in a sensitive subgroup.

   Any existing RfD or RfC can be used in this exercise. Alternatively, an RfD or RfC can be developed in the usual fashion using existing EPA methods, including choices of critical effect, No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL) or benchmark dose (BMD) as possible points of departure, and judgments of the need for one or more of EPA's standard 5 uncertainty factors based on the availability of data.

3. **Please provide an example/case study, which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

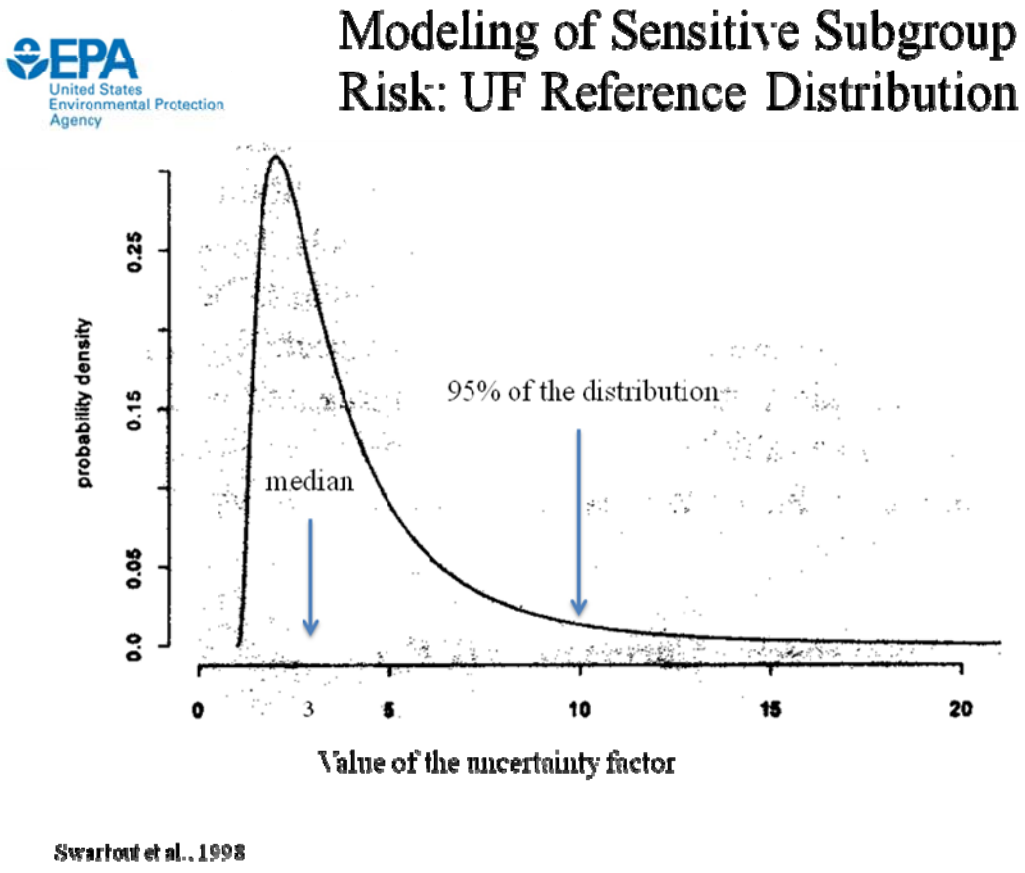
   The case study will use 10 RfDs and RfCs selected at random from EPA's Integrated Risk Information System (IRIS). Uncertainty factors used for these RfD/RfCs will be studied and a probabilistic determination of each RfD/RfC will be made based the

[1] Swartout, J., P. Price, M. Dourson, H. Carlson-Lynch and R. Keenan. 1998. A Probabilistic Framework for the Reference Dose. Risk Analysis. 18(3):271-282.

reference uncertainty factor distribution given by Swartout et al. (1998) and shown in the figure below.[2]

A composite uncertainty factor distribution will then be created for each RfD/RfC, which will allow the determination of the likelihood that a sensitive subgroup will be judged to have the critical effect at any dose in excess of the RfD/RfC. Swartout et al. (1998) show probabilities at various default uncertainty factors as seen in their Table II shown below, from which these determinations can be made.

Figure 2. Reference uncertainty factor distribution – UF_R.



[2] Uncertainty factors based on actual data, such as a Chemical Specific Adjustment Factor (CSAF), will use the probabilistic value of the CSAF. For example, if EPA's boron RfD is selected, then the data underlying the within-human and experimental animal to human uncertainty factors will be obtained and the distribution of these factors will be used directly.

EPA United States Environmental Protection Agency

Table II. Selected Percentiles for Combinations of U_R[a]: Pr($U_R \leq 10$) = 0.95

Percentile	U_R	U_R^2	U_R^3	U_R^4	U_R^5
Default Factor:	10	100	1000	3000	10,000
50	3.16	11	37	127	433
95	10.0	51	234	1,040	4,440
99	17.3	104	544	2,700	12,700

A

B

What does the predicted response mean?

A. The value of the composite uncertainty factor will differ from the default with a selected probability, e.g., 95%.
B. The probability of differing combinations of default uncertainty factors will not be the same.

A conservative estimate of the risk of the critical effect occurring in a sensitive subgroup can be made by subtracting the associated percentile from a value of 1.0. For example, if a composite factor of 10 is used, then a 5% chance exists that a sensitive subgroup will be judged to show the critical effect (i.e., 1.0 – 0.95 = 0.05, or 5%); if a composite factor of 100 is used, then this same chance approximates 1% (i.e., 1.0 – 0.99 = 0.01, or 1%). However, this chance does not specify the number of individuals responding. In addition, the composite uncertainty factor will have a probabilistic form at doses both above and below the RfD/RfC that would vary, since composite uncertainty factors vary in their composition of default values.

Proposed team to develop case study

Michael Dourson, Toxicology Excellence for Risk Assessment
Tba: U.S. Environmental Protection Agency

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail

Natalia Foronda
New Zealand Ministry of Health
natalia_foronda@moh.govt.nz

1. Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).

Assess to what extent young children are susceptible to the toxic effects of hazardous substances.

2. Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).

The Integrated Exposure Uptake Biokinetic (IEUBK) Model is proposed to be used. The IEUBK is a classical multicompartmental pharmacokinetics model linked to an exposure and probabilistic model of blood lead concentration distributions in populations of children ages 0-7 years.

The exposures from air, food, water, soil, and dust are modelled independently by several routes. Amounts of lead absorbed are modelled independently for air, food, water, soil/dust, then combined as a single input to the blood plasma reservoir of the body. Lead in the plasma reservoir, which includes extracellular fluids, is mathematically allocated to all tissues of the body using age-specific biokinetic parameters. The model calculation provides the estimate for blood lead concentration for that age. This value is treated as the geometric mean of possible values for a single child, or the geometric mean of expected values for a population of children exposed to the same lead concentrations.

References:
EPA.1994. Guidance manual for the integrated exposure uptake biokinetic model for lead in children. U.S. Environmental Protection Agency. EPA540R93081, PB93963510.

White PD, Van Leeuwen P, Davis BD, et al. 1998. The conceptual structure of the integrated exposure uptake biokinetic model for lead in children. Environmental Health Perspective 106:1513-1530.

3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

The NZ Health Act current non-occupational notifiable blood lead level is 10 μg/dL (0.48 μmol/L). This is the level of lead in blood that requires a GP to inform the local medical officer of health that their patient has lead poisoning. Actual notifications of raised blood levels are relatively frequent, but notification is not an accurate reflection of the problem because many cases go undetected.

The US Centres for Disease Control and Prevention and the World Health Organization have identified 0.48 μmol/L as a level of concern for children. Although clinical symptoms of lead toxicity generally become apparent at blood lead concentrations above 3.38 umol/l, impaired cognition, attention and language function have been observed in children at blood lead levels previously thought to be harmless, with effects now becoming visible below 0.48 μmol/L. In addition, most children suffering from elevated blood lead levels have no clear symptoms.

There is as yet no available epidemiological evidence of a lower threshold or "no-effect level" below which the lead/IQ association is *not* found. However, setting a level below 0.48 μmol/L would be counterproductive since no effective clinical or public health interventions have been identified below this level.

A comprehensive literature search will be conducted covering various exposure pathways, exposure levels, adverse effects observed, etc in young children. The data collected will be used in modeling which can then be used further in ascertaining at what levels of environmental lead concentrations children will have risks of elevated BLL in excess of the notifiable level.

The results from this study will determine whether or not a blood study is warranted in the future. White et al. (1998) stated in their report "Why use a model to estimate environmental lead risks when you can measure children's blood lead levels directly? A first answer is that public health concerns dictate the prevention and minimization of exposure to lead, particularly for young children. When lead is measured in children's blood, exposure has already occurred. Furthermore, although thorough community blood lead studies can provide very useful data, they are not simple or inexpensive to conduct and interpret. Relatively large numbers of subjects are needed to obtain estimates of community risks, and reliable studies need to be based on community consensus or random sampling approaches that achieve high response rates."

4. Proposed team to develop case study

Natalia Foronda, Ph.D., Senior Advisor (Toxicology), Ministry of Health

Deborah Read, Public Health Physician, Ministry of Health

Barry Borman, Ph.D. Epidemiologist, Associate Professor, Massey University

TERA as needed

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:
Roberta L. Grant
Toxicology Division, Texas Commission on Environmental Quality
rgrant@tceq.state.tx.us

1. Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).

A toxicity assessment is needed to develop scientifically credible, acute exposure guideline levels (AEGLs) for once-in-a-lifetime short-term exposures to airborne concentrations of highly toxic chemicals. AEGL values are developed for three different health effect end point tiers (discomfort = AEGL-1 threshold; disability = AEGL-2 threshold, and death = AEGL-3 threshold) (Figure 1) at different durations of exposure (10 minutes; 30 minutes; 1 hour; 4 hours; and 8 hours) within the constraints of data availability, resources, and time. The AEGL values are intended to protect the general public, including susceptible individuals such as infants, children, the elderly, persons with asthma, and those with other illnesses. These guideline levels are needed for a wide range of chemical emergency response, planning, and prevention programs. More specifically, the AEGL values will be used for conducting various risk assessments to aid in the development of emergency preparedness and prevention plans, as well as real-time emergency response actions. These applications may include EPA's SARA Title III Section 302-304 emergency planning program, the U.S. Clean Air Act Amendments (CAAA) Section 112(r) accident prevention program, and the remediation of Superfund sites program; the Department of Energy's (DOE's) environmental restoration, waste management, waste transport, and fixed facility programs; the Department of Transportation's (DOT's) emergency waste response program; the Department of Defense's (DOD's) environmental restoration, waste management, and fixed facility programs; ATSDR's health consultation and risk assessment programs; NIOSH's and the Occupational Safety and Health Administration's (OSHA's) regulations and guidelines for workplace exposure; state CAA Section 112(b) programs and other state programs; and private-sector programs, such as the AIHA-ERPG and the American Chemistry Council's Chemtrec programs. AEGLs may be used as a screening approach during a chemical accident. During an emergency release, modeling and/or air monitoring are performed by emergency responders and compared to appropriate AEGL values to determine what course of action to take to minimize health effects (i.e., shelter in place, emergency evacuation, etc.).

AEGL values must be as close to reality as possible. If unrealistically conservative values are developed they will not be used by those who need them or seriously erroneous conclusions reached. For example, in a triage situation responders might assume that people exposed to concentrations above an AEGL-3 level will be dead. Response will be focused on people exposed to lower levels because of the assumption that individuals in the AEGL-3 zone will be beyond help. If AEGL values are developed which are overly conservative, response efforts may be misdirected.

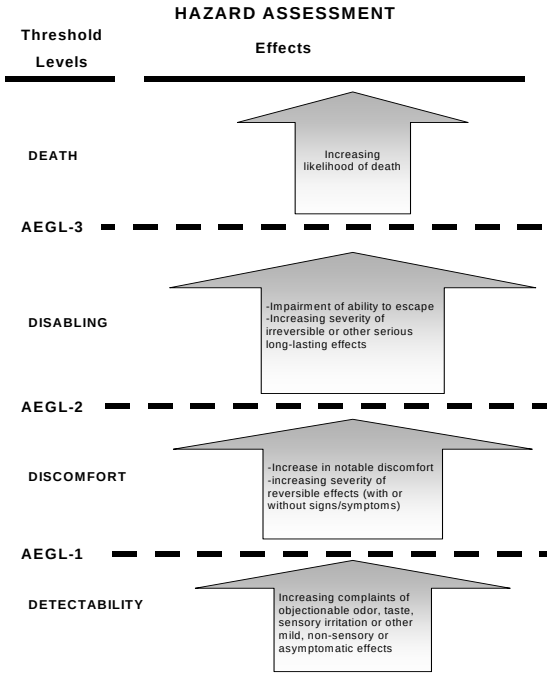


Figure 1. Illustration of different effect levels for Acute Exposure Guideline Levels (AEGLs). (Figure 1-1 from NRC (2001)).

2. Please describe the proposed method (1-3 pages). Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).

This method will use hazard identification and dose-response assessment (i.e., a toxicity assessment) based on available toxicity data for the example chemical based on guideline methods in NRC (2001) to develop AEGL values. Briefly, the appropriate threshold concentration levels for each of the three health effect endpoints (AEGL-1, -2 and -3) (Figure 1) are identified or derived. Subsequently, interspecies and intraspecies adjustments are applied as well as other adjustments for uncertainty followed by time-scaling the resultant values to obtain the proper AEGL exposure periods (10-min, 30-,min, 1-hr, 4, and 8-hrs). Additional information on the Standing Operating Procedures (SOP) for developing AEGLs is found at http://www.epa.gov/oppt/aegl/pubs/sop.htm.

3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

The proposed case study is development of AEGL-1, AEGL -2, and AEGL -3 values for ethylbenzene (AEGL 2008). Ethylbenzene is a flammable liquid that is insoluble in water and miscible with most organic solvents (O'Neil et al. 2001). The chemical is used mainly in the production of styrene with other uses less than 1% of the total ethylbenzene produced (ECETOC 1986). In 2001, world demand for ethylbenzene was about 23 million metric tons. Use of the chemical is projected to increase at an annual rate of 4.6% from 2001-2006 (Ring and Linak 2002).

Experimental data on the effects of ethylbenzene on humans showed irritation at high concentrations for short durations but possible CNS effects with lower concentrations for longer durations. Limited data suggest that the young animal is the most susceptible to effects of ethylbenzene and that this susceptibility is dependent on the body weight of the animal. Signs of irritation were observed in

laboratory animals at concentrations >1000 ppm. Narcosis developed at ~2000 ppm. The cochlear ducts in the inner ear may be a target organ following repeated exposure, but no data were found which indicate ototoxicity after a single exposure to ethylbenzene. Decreased body weight gain occurred in animals exposed repeatedly.

Experimental data on the effects of ethylbenzene on humans were available for the derivation of AEGL-1 values. No problems were reported by nine individuals exposed to 100 ppm for 8 hours. However, during exposure of eleven individuals to 180 ppm for 8 hours, some complained of irritation of the upper respiratory tract and eye and headache and sleepiness towards the end of the exposure; transient feelings of drunkenness were also reported (Bardodej and Bardodejova 1961). Motor activity in rats increased following exposures to 400-1500 ppm for four hours then decreased – perhaps indicative of CNS depression – at higher concentrations (Molnár et al. 1986). A number of experimental studies in adult animals indicate that clinical signs and systemic effects are not observed at concentrations less than 1000 ppm following single or repeated exposures. These concentrations are much greater than those causing effects in humans. Therefore, a concentration of 100 ppm for 8 hours was chosen as the point of departure for derivation of AEGL-1 values. This is the highest concentration in humans which did not produce clinical signs after a single exposure. A total uncertainty factor of 3 was used which includes 3 for intraspecies extrapolation because the point of departure was a no effect level for irritation and is below that which would cause CNS effects. An intraspecies UF of 3 is appropriate because direct acting irritant effects at the portal of entry are not expected to vary between individuals. The same UF is appropriate for mild CNS effects (see rationale below). Because the point of departure is below that causing systemic effects, time scaling was not performed.

The AEGL-2 is based upon the highest non-narcotic level in rats. Motor activity was monitored in male CFY rats during a 4-hour exposure to 400-2180 ppm ethylbenzene (Molnár et al. 1986). Exposure resulted in a biphasic response with increased activity between 400-1500 ppm followed by a decrease in activity at higher concentrations. A concentration of 2180 ppm was listed as the minimum narcotic concentration with 1500 ppm the highest non-narcotic concentration. It is assumed that the central nervous system response observed following ethylbenzene exposure is directly related to the concentration of parent material reaching the brain, and that venous blood concentrations correlate with brain concentrations. Therefore, the venous blood concentration (Cv) of ethylbenzene following a 4-hour exposure to 1500 ppm would be expected to provide an internal dose measurement correlating with the no effect for a narcotic response. Using a physiologically-based pharmacokinetic (PBPK) model, the internal dose (Cv) producing the highest non-narcotic condition in rats was determined. Then, the human PBPK model was run for each defined AEGL time point to determine the equivalent exposure concentration producing the target Cv. It is acknowledged that the resulting AEGL 2 values may not be protective of ototoxicity which occurs after repeated exposures, however no data are available to assess this endpoint following a single exposure to ethylbenzene.

Human exposure data relevant to derivation of AEGL-3 values were not available. The most appropriate animal data relevant to derivation of AEGL-3 values are those of Andersson et al. (1981). The highest non-lethal exposure of adult rats to 2000 ppm, 6 hours/day for 3 days was used as the basis for deriving the 10-min, 30-min, 1-hour, 4-hour, and 8-hour AEGL-3 values. As for the AEGL-2, it is assumed that the central nervous system effects observed following ethylbenzene exposure are directly related to the concentration of parent material reaching the brain. Therefore, PBPK modeling was again used to calculate the internal dose (Cv) correlating with an exposure to 2000 ppm for 6 hours which was the highest non-lethal concentration. The human PBPK model was then run for each defined AEGL time point to determine the equivalent exposure concentration producing the target Cv.

A total uncertainty factor of 3 was applied to the AEGL-2 and -3 dose metrics. An interspecies uncertainty factor of 1 was applied because PBPK modeling reduced the toxicokinetic component of the uncertainty factor to 1 and the pharmacodynamic component is also reduced to 1 because it appears similar exposure effects (central nervous system effects) occur in humans and animals. An intraspecies uncertainty factor of 3 was applied because the mode of action of ethylbenzene is similar to anaesthetic chemicals. The minimum alveolar concentration (MAC -30 produces a lack of motor response in 50% of individuals exposed to that concentration) for different age groups from newborns to the elderly and pregnant women has been studied for a number of anaesthetic gases. It varies from 2-3 fold (NRC 2001).

The calculated values are listed in the table below.

Summary of AEGL Values for Ethylbenzene

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	33 ppm (144 mg/m^3)	33 ppm (144 mg/m^3)	33 ppm (144 mg/m^3)	33 ppm (144 mg/m^3)	33 ppm (144 mg/m^3)	Highest no effect level in humans (Bardodej and Bardodejova 1961)
AEGL-2 (Disabling)	2900 ppm (13,000 mg/m^3)	1600 ppm (7000 mg/m^3)	1100 ppm (4800 mg/m^3)	660 ppm (2900 mg/m^3)	580 ppm (2500 mg/m^3)	No effect level for narcosis in rats (Molnár et al. 1986)
AEGL-3 (Lethal)	4700 ppm (20,400 mg/m^3)	2600 ppm (11,000 mg/m^3)	1800 ppm (7800 mg/m^3)	1000 ppm (4400 mg/m^3)	910 ppm (4000 mg/m^3)	Highest non-lethality in rats (Andersson et al. 1981)

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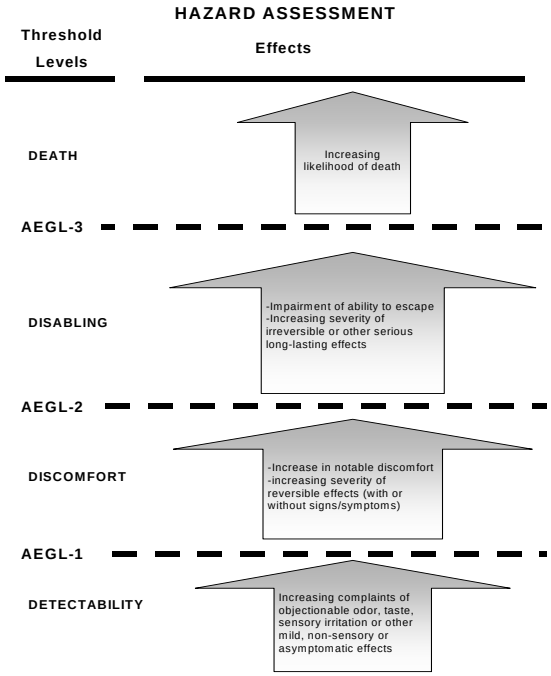

Figure 1. Illustration of different effect levels for Acute Exposure Guideline Levels (AEGLs). (Figure 1-1 from NRC (2001)).

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3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

The proposed case study is development of AEGL-1, AEGL -2, and AEGL -3 values for silane (AEGL 2007). Silane (CAS No. 7803-62-5) is a colorless gas that has a repulsive odor. It is used in industry in the microelectronics and is a source of hyperpure silicon used for semiconductors (Arkles 2000). Limited data are available regarding the toxicity of silane in humans or laboratory animals. Silane can ignite spontaneously in room air and can cause explosions making it difficult to conduct studies safely.

AEGL -1 values were determined from a study in which male mice were exposed to 1000 ppm silane for 1, 2, 4 or 8 hours. The NOAEL for irritation was 1,000 ppm (Omae et al. 1992). No

effects were observed on mortality, hematology, clinical chemistry or histopathology. Clinical signs in treated animals included increased washing of the face and lower abdominal area after exposure. The only finding was a slight increase in inflammatory nasal cells in mice exposed to 1000 ppm silane for 6 hours/day, 5 days/week over 4 weeks. Therefore, 1000 ppm will be the point-of-departure for the 10-min., 30-min and 1 hour AEGL-1 values with no time-scaling. Derivation of 4 and 8 hour values from this data is not recommended as it would result in AEGL-1 values greater than the 4 and 8 hour AEGL-2 values. A total uncertainty factor of 10 was used, 3 for both interspecies and intraspecies because the only effect observed was mild irritation and this response is not expected to vary greatly among species or humans.

AEGL-2 values were derived from a 4 hour acute inhalation study in mice (Takebayashi 1993). In mice exposed to 2500 ppm for four hours, renal lesions observed two days post-exposure resolved within two weeks. At the next higher concentration, 5000 ppm, renal lesions were noted after both the two day and two week observations, making 2500 ppm the NOEL for irreversible effects at 4 hours. Time-scaling was performed using the formula $C^n \times t = k$ where n values range from 0.8 to 3.5 (ten Berge et al. 1986). When data are limited, the Standing Operating Procedure (SOP) for Developing AEGLs for Hazardous Chemicals (NRC 2001) states that the default value of n = 1 is used when extrapolating from shorter to longer study durations and n = 3 is used when extrapolating from longer to shorter durations. Since extrapolating from 4 hours to 10 minutes is not recommended, the 30 minute value was adopted as the 10 minute value. A total uncertainty factor of 30 was used, 3 for interspecies and 10 for intraspecies. An interspecies value of 3 was used because an LC_{50} study (MacEwen and Vernot 1972) identified the mouse as being more sensitive than the rat. The intraspecies uncertainty factor was set at the default value of 10 as there is no data to estimate human variability and the chemical was not acting as a direct irritant.

AEGL-3 values were based on a 4 hour mouse inhalation study; 5000 ppm was the concentration that induced irreversible microscopic renal lesions and was the no-effect level for lethality (Takebayashi 1993). A single exposure to the highest level tested, 10,000 ppm, caused mortality in 6/8 mice observed for two weeks post-exposure. Time-scaling was performed using the formula $C^n \times t = k$ where n values range from 0.8 to 3.5 (ten Berge et al. 1986). Scaling was performed using n =3 for extrapolating to the 30 minute and 1 hour time point and n = 1 for extrapolating to 8 hours. Since extrapolating from 4 hours to 10 minutes is not recommended, the 30 minute value was adopted as the 10 minute value. A total uncertainty factor of 30 was used, 3 for interspecies and 10 for intraspecies. An interspecies value of 3 was used because an LC_{50} study (MacEwen and Vernot 1972) identified the mouse as being more sensitive than the rat. The intraspecies uncertainty factor was set at the default value of 10 as there is no data to estimate human variability and the chemical was not acting as a direct irritant.

The AEGL-1, AEGL-2 and AEGL-3 derived values are listed in the table below.

Summary of AEGL values for Silane in ppm (mg/m^3)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	100 ppm (130 mg/m^3)	100 ppm (130 mg/m^3)	100 ppm (130 mg/m^3)	NR	NR	No-effect level (Omae et al 1993)
AEGL-2 (Disabling)	170 ppm (220 mg/m^3)	170 ppm (220 mg/m^3)	130 ppm (170 mg/m^3)	80 ppm (100 mg/m^3)	42 ppm (55 mg/m^3)	Concentration with reversible renal lesions (Takebayashi 1993)
AEGL-3 (Lethality)	300 ppm (400 mg/m^3)	300 ppm (400 mg/m^3)	270 ppm (350 mg/m^3)	170 ppm (270 mg/m^3)	80 ppm (100 mg/m^3)	No-effect level for lethality, irreversible renal lesions (Takebayashi 1993)

ppm = parts per million, m/m^3 = milligrams per cubic meter

References

Acute Exposure Guideline Levels. 2007. Acute Exposure Guideline Levels (AEGLs) for silane (CAS Reg. No. 7803-62-5). Interim. Available from: http://www.epa.gov/oppt/aegl/

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Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:

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1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

An improved capacity is needed to make inferences from NTP bioassay and genotoxicity data about the potential human cancer risks associated with environmentally relevant exposures. The example seeks to explore risk assessment options for a metal that is ubiquitous in soil and for which the results of a recent NTP bioassay and linear extrapolation were used to develop a cancer slope factor assuming a mutagenic mode of action.

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

A study is presently underway that to address data gaps in the knowledge of the MOA and answer the questions raised by the NTP bioassay results. The MOA study is expected to be complete in by the beginning of 2011. The timing of this work is consistent with the schedule of Alliance for Risk Assessment Silver Book workshops and should provide an example of the potential for biological data about the MOA to reduce uncertainty in a risk assessment. The richness of the data anticipated from the MOA study will enable a detailed exploration of the Silver Book methods.

3. **Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

A recent National Toxicology Program bioassay of hexavalent chromium [Cr(VI)] exposure from drinking water using both rats and mice could not establish concordance of tumor sites between the two test species or between either test species and humans. There are alternatives to a strictly mutagenic MOA – two of these are genomic instability and oxidative stress. Genomic instability leads to cancer in humans and is produced by Cr(VI) in many systems (Lengauer et al., 1998; Holmes et al., 2008). Oxidative stress is reflected by increases in anti-oxidant enzymes in rat small intestine and mouse liver in response to hexavalent chromium (Arivarasu et al., 2008; Wang et al., 2006). p53 has long been know to control the cell cycle, and oxidative stress by itself is a strong inducer of p53 (Tomko et al., 2006). The oxidative stress caused by Cr(VI) has also been shown to activate a variety of transcription factors, NF-κB, AP-1 and HIF-1 as well as p53. These factors regulate the cell cycle and are very likely involved in chromium carcinogenesis.

The questions to be addressed by the MOA study are:

1. There was a dose-related increase in small intestinal tumors in mice and a dose-related increase in oral tumors in rats. Why is there a lack of concordance of tumor site between rodent species?

2. Why do tumors in mice appear more distally in GI tract with higher drinking water concentrations of Cr(VI)?
3. If the Cr(VI) MOA is solely mutagenic, then why do no tumors occur in the mouth, stomach or forestomach of mice?
4. Intestinal tumors were observed only in mice experiencing prolonged hyperplasia? What is the relationship between hyperplasia and tumors?
5. Is there a Cr(VI) dose that does not cause intestinal hyperplasia in mice; are doses at or below such a dose carcinogenic?
6. Is there a dose at which Cr(VI) reduction in the stomach will be sufficient to prevent key events required for tumorigenesis in the small intestine? How does this vary between the two test species and between the two test species and humans?
7. How are findings relevant to humans who are exposed at much lower levels?

The MOA Study design was peer reviewed by an independent Expert Panel convened by TERA in July of 2009. The panel's recommendations were incorporated into the MOA Study. The study will include:

1. Histopathology of target tissues, as well as two-year NTP results, to anchor biochemical and genomic changes to phenotypic results;
2. Gene microarray studies to measure transcriptional changes in oral, duodenal, and jejunal epithelial cells;
3. Biochemical analyses to measure oxidative stress, inflammation, and the occurrence of Cr-DNA adducts;
4. Toxicokinetic studies to measure tissue Cr levels in 13 tissues of each species, including mucosa and submucosa of target tissues, to provide data for PBPK models;
5. *In vivo* mutation analyses in target tissues to determine the extent to which DNA damage leads to mutation; and
6. High Content Imaging Analysis *in vitro* to assess differences between rodents and humans.

The dataset resulting from the Cr(VI) MOA study will provide a unique opportunity to "ground-truth" the methods in the Silver Book.

Arivarasu NA, Fatima S, Mahmood R. 2008. Oral administration of potassium dichromate inhibits brush border membrane enzymes and alters anti-oxidant status of rat intestine. Arch Toxicol 82(12):951-8.

Holmes AL, Wise SS, Wise JP, Sr. 2008. Carcinogenicity of hexavalent chromium. Indian J Med Res 128(4):353-72.

Lengauer C, Kinzler KW, Vogelstein B. 1998. Genetic instabilities in human cancers. Nature 396(6712):643-9.

Tomko RJ, Jr., Bansal P, Lazo JS. 2006. Airing out an antioxidant role for the tumor suppressor p53. Mol Interv 6(1):23-5,

Wang XF, Lou XM, Shen Y, Xing ML, Xu LH. 2010. Apoptotic-related protein changes induced by hexavalent chromium in mice liver. Environ Toxicol 25(1):77-82.

Zhitkovich A, Peterson-Roth E, Reynolds M. 2005. Killing of chromium-damaged cells by mismatch repair and its relevance to carcinogenesis. Cell Cycle 4(8):1050-2.

4. Proposed team to develop case study (desired, but optional)

Ted Simon, Deborah Barsotti, Mark Harris, Deborah Proctor, Chad Thompson, Laurie Haws

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:
Michael Dourson
Toxicology Excellence for Risk Assessment (*TERA*)
dourson@tera.org

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

   Ubiquitous food contaminants demand careful dose response assessment prior to judging whether a significant part of the diet is with significant risk.

   Improved cancer dose response assessment based on EPA (2005) cancer guidelines with multiple modes of action (MOAs). Page 3-22 of EPA (2005) states that:

   > "If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur."

   However, EPA does not give any guidance on how to proceed with such decoupling. This proposal offers one way to consider it.

2. **Please describe the proposed method (1-3 pages). Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   This approach is an extension of EPA's benchmark dose (BMD) method that allows the development of differing slopes of cancer dose response curves in different parts of the dose response range. First, a MOA analysis is needed to identify the various components (e.g., mutagenicity and hormonal action) that contribute to the overall carcinogenic response. Second, a model is sought within EPA recommendations that allows a flexible dose-response function patterning the differing MOAs. The suggested method is a straightforward application of one or more of the models found in EPA's cancer guidelines that have this flexibility (e.g., the multistage and probit). Several models will be explored.

   The appropriate BMD will be chosen in the usual fashion using existing EPA software and criteria, including p-values, AIC, residuals, BMD to BMDL ratios and visual inspection. However, the chosen model will have to comply with these criteria in each part of the dose response curve associated with a different MOAs.

3. Please provide an example/case study, which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

The case study will use the analysis of acrylamide's thyroid carcinogenicity as published by Dourson et al. (2008). In addition, results from a hybrid model will be further developed. Two selected tables and figures are shown below from this publication to indicate some of the expected results.

Proposed team to develop case study

Michael Dourson, Toxicology Excellence for Risk Assessment
Tba: Biomathematician

References:

Dourson, M., Hertzberg, R., Allen, B., Haber, L., Parker, A., Kroner, O., Maier, A. and Kohrman, M. 2008. Evidence-Based Dose Response Assessment for Thyroid Tumorigenesis from Acrylamide. Regulatory Toxicology and Pharmacology 52 (2008) 264–289.

U.S. Environmental Protection Agency. 2005. Guidelines for carcinogen risk assessment. Washington D.C. EPA/630/P-03/001B.

Table 4. Multistage model estimates of slope factors (SF) for the rat thyroid tumor data. BMD/L values are in mg/kg-day; SF values are in (mg/kg-day)$^{-1}$.

Data set[a]	SF at BMDL 10 (all data)	SF at BMDL 02 (all data)	SF at BMDL 02 (low dose data)[b]
Johnson female	0.067	0.069	0.11
Freidman female	0.11	0.11	c
Johnson male	0.085	0.089	d
Friedman male	0.13	0.14	0.15
Pooled female	0.086	0.089	d
Pooled male	0.095	0.099	0.11
Pooled all	0.083	0.087	0.088

a. Friedman, et al., 1995; Johnson, et al., 1986.
b. Only the data with dose<1.0 were modeled.
c. Only one dose<1.0 in Friedman female study.
d. BMD02 values are not determined by BMDS with low dose data because of unacceptable extrapolation (BMD larger than three times maximum input dose).

Figure 2a. Multistage model fitted to pooled-all thyroid tumor data, showing little change in slope between the low and high dose regions.

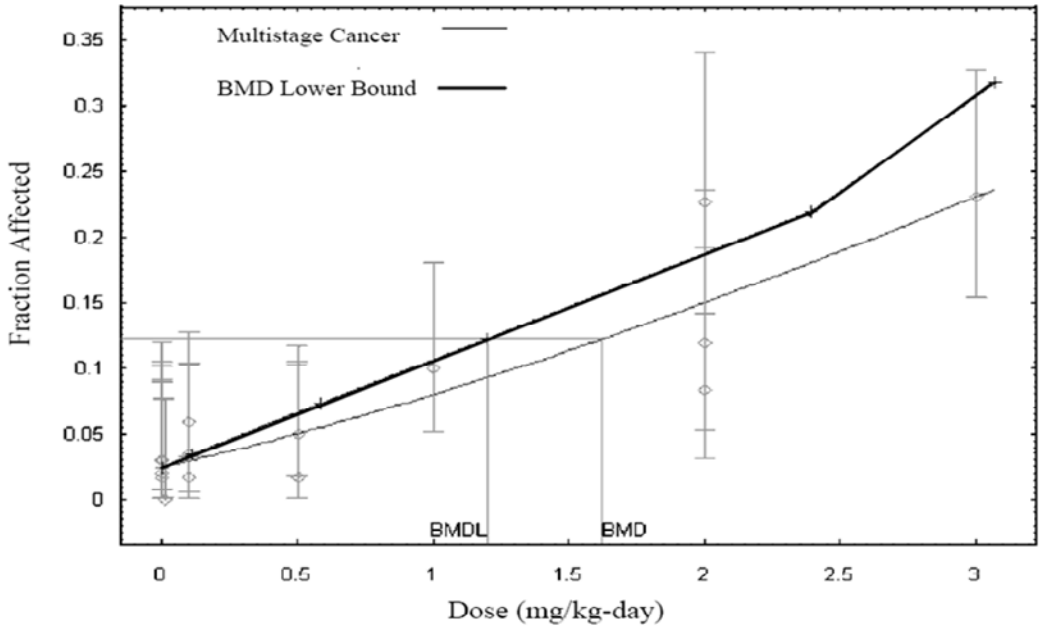
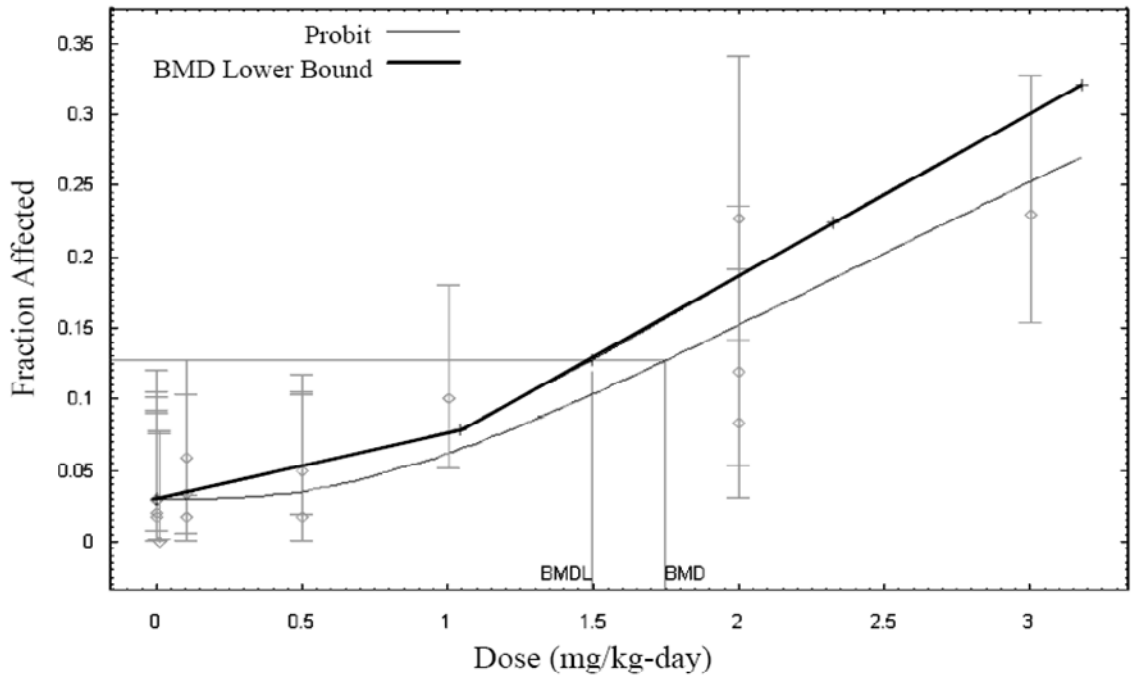


Table 5. Probit model estimates of slope factors (SF) for pooled male and female rat data on thyroid tumors. BMD/L values are in mg/kg-day; SF values are in (mg/kg-day)$^{-1}$.

Data set[a]	BMD 02	SF at BMD 02	BMDL 02	SF at BMDL 02
Pooled female	0.82	0.024	0.67	0.030
Pooled male	0.97	0.021	0.58	0.034
Pooled all	0.81	0.025	0.69	0.029
	BMD 10	**SF at BMD 10**	**BMDL 10**	**SF at BMDL 10**
Pooled female	1.8	0.057	1.5	0.069
Pooled male	1.7	0.059	1.3	0.079
Pooled all	1.7	0.057	1.5	0.067

Figure 2b. Probit model fitted to pooled-all thyroid tumor data, showing differing slopes between the low and high dose regions.



Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:
Michael Dourson
Toxicology Excellence for Risk Assessment (*TERA*)
dourson@tera.org

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

   For the purposes of conducting a cost-benefit analysis, estimate the median and upper bound fraction of people expected to have an adverse noncancer effect at any specified exposure level.

2. **Please describe the proposed method (1-3 pages). Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   This method is an extension of the benchmark dose (BMD) that allows the development of probabilities of adverse effect at any dose at or above a threshold of one molecule. Risks are developed by analogy to the default approach recommended for cancer toxicity (EPA, 2005), by extending a straight line from the chosen BMDL, using the recommended procedure for extrapolation from experimental animals to humans when appropriate to develop a human equivalent dose or concentration (HED or HEC).

   The appropriate BMD is chosen in the usual fashion using existing EPA software and criteria, including p-values, AIC, residuals, BMD to BMDL ratios and visual inspection. The data are modeled to an appropriate point of departure using the usual judgment; lifetime HEDs associate with both the BMD and BMDL are then estimated; and straight lines are then drawn from both the HED and HEC to zero. Upper bound and expected risk are then read from the graph.

   This procedure makes at least two assumptions that should be carefully check against available data. Assumptions include:
   - The threshold for adverse effect is one molecule; if the chemical's Mode of Action (MOA) can be envisioned to have a threshold greater than one molecule, then this procedure may not be appropriate.
   - A linear extrapolation from the point of departure to zero is an appropriate form of the expected adverse response; if dose dependent transitions in the development of an adverse effect, or if non-adverse precursors, such as adaptation or hormesis are anticipated, then this procedure may not be appropriate.

The suggested procedure needs sufficient data for development of BMDs and rests on the acceptance of two or more assumptions that are controversial. However, the procedure can be modified to incorporate BMD models that include a threshold term greater than zero, and its ease of use might be helpful for problem formulations that include a screening component.

3. **Please provide an example/case study that demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

   The case study will use 10 RfDs and RfCs selected at random from EPA's Integrated Risk Information System (IRIS), which have been based on BMDLs/BMCLs. Uncertainty factors used for these RfD/RfCs will be studied and adjustments will be made to estimate lifetime HEC BMDs/BMCs and HEC BMDLs/BMCLs. A straight line will be applied to these HECs to zero and probabilities will be determined at relevant doses/concentrations.

Proposed team to develop case study

Michael Dourson, Toxicology Excellence for Risk Assessment
Tba - California Environmental Protection Agency
Tba - Connecticut Dept of Public Health

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:
Michael Dourson
Toxicology Excellence for Risk Assessment (*TERA*)
dourson@tera.org

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

   For the purposes of conducting a cost-benefit analysis or determining the impact of overrunning "risk cups," estimate the likely risk above some measure of the "safe" dose, such as an RfD. This risk can be measured as either:
   - an estimate of the number of people expected to have an unspecified adverse noncancer effect at a specified exposure level, or
   - as the probability of a dose group showing an effect of specified severity.

2. **Please describe the proposed method (1-3 pages). Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   Categorical regression is a well-established method that has utility in using a variety of toxicology data in an integrated fashion (e.g.,Hertzberg and Dourson, 1993). This method has an added advantage of integration of results over time, and has been used to analyze air toxics (e.g., Guth et al., 1997).

   Toxicology data are evaluated in the usual fashion using existing methods, such as EPA (2002) or Meek et al. (1994). Effects are categorized into 3 or more groups based on judgments of general severity, such as no effect, non-adverse effect, adverse effect, or frank effect. Other scoring systems are possible, and even encouraged. Care is used to determine whether individuals within a dose group can be assigned into separate categories. Otherwise the dose group is categorized as a whole, and this datum becomes the subject of the regression. Individuals or dose groups are then modeled using existing software provided by EPA (2000), and then two different interpretations of the y-axis are used depending on whether the modeled data were based on individuals or dose groups.

   Both interpretations will be explored using published evaluations, and potentially new information and the problem formulation will be refined appropriately. For example, some datasets may be more appropriate for screening-level estimates of risk above the RfD, while others may be more appropriate for more comprehensive estimates.

3. Please provide an example/case study that demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

The case study will use published evaluations for 6 pesticides out of EPA's extensive database, and perhaps new data. Selected figures tables and figures below from two publications show some of the expected results.

Proposed team to develop case study

Michael Dourson, Toxicology Excellence for Risk Assessment
Tba: U.S. Environmental Protection Agency

Aldicarb Clinical Studies

Frequency of Clinical Signs or Blood Cholinesterase				
Study	**Dose (mg/kg-day)**	**Group Size**	**Clinical Signs**	**Blood Cholinesterase Inhibition[a]**
Haines, 1971	0.025	4	1 Apprehension	4 Whole blood
	0.05	4	1 Runny nose[c]	4 Whole blood
	0.10	4	4 Weakness and sweating, Nausea in 2 individuals	4 Whole blood
Wyld et al., 1992[b]	0	22	0	0 Plasma & 0 RBC
	0.010	8	2 Headaches[c]	0 Plasma & 0 RBC
	0.025	12	1 Sweating	12 Plasma & 11 RBC
	0.050	12	1 Sweating	1 Plasma & 1 RBC
	0.06	1	1 Sweating	1 Plasma & 1 RBC
	0.075	3	1 Lightheadedness	3 Plasma & 3 RBC

Dourson, et al., 199[illegible]

Effect Categories of Aldicarb Exposure in Humans

Frequency of Categories of Effect Associated with Aldicarb Exposure in Humans						
Study	Dose (mg/kg/day)	Group Size	Frequency of Responders within Categories of:			
			NO Effects	Non-adverse Effects	Adverse Effects	Frank Effects
Wyld	0.0	22	**22 (22)**	0 (0)	0 (0)	0 (0)
Wyld	0.010	8	**8 (0)**	0 (0)	0 (0)	0 (0)
Wyld	0.025	12	0 (0)	**8 (11)**	**4 (1)**	0 (0)
Haines	0.025	4	0 (0)	**0 (3)**	**4 (1)**	0 (0)
Wyld	0.50	12	0 (0)	**1 (11)**	**11 (1)**	0 (0)
Haines	0.50	4	0 (0)	**0 (4)**	**4 (0)**	0 (0)
Wyld	0.075	4	0 (0)	**0 (2)**	**4 (2)**	0 (0)
Haines	0.10	4	0 (0)	0 (0)	**2 (2)**	**2 (2)**

Probabilities in the graph below indicate the number of individuals responding, since the incoming data was based on individuals.

Probability of Effects with Aldicarb

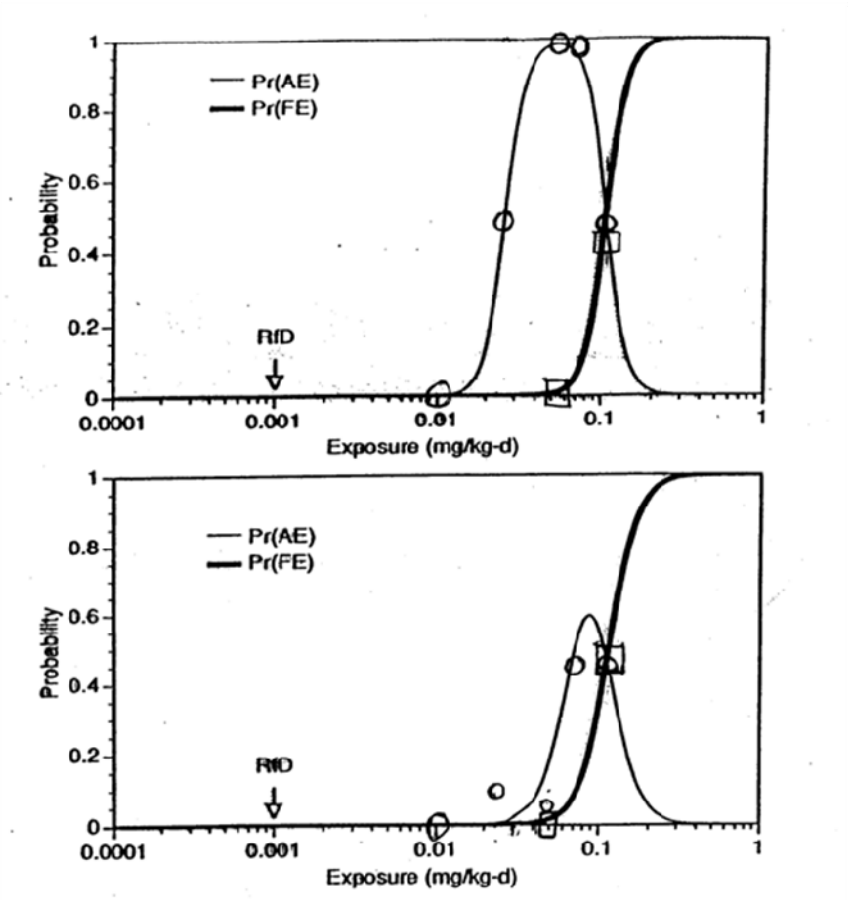


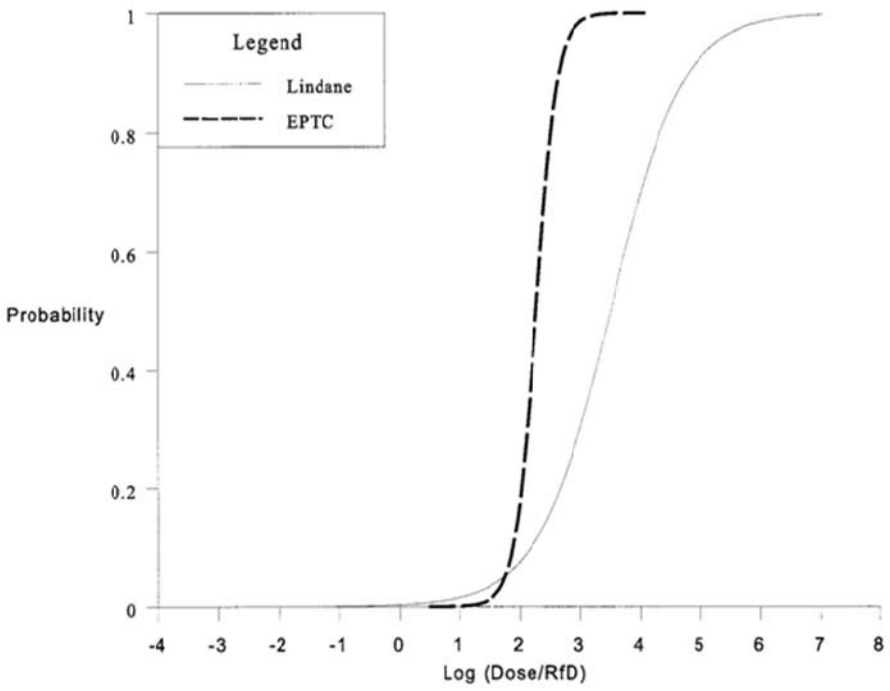
TABLE 1
Frequency Distribution (%) of Data Records Among Response Categories for Five Pesticides

Pesticide	Response categories				Total number of data records
	NOEL	NOAEL	AEL	FEL	
Diazinon	17.4	16.5	52.1	14.0	121
	6.5	18.2	62.3	13.0	77
Disulfoton	6.0	14.0	68.0	12.0	50
	2.1	14.9	70.2	12.8	47
EPTC	19.7	32.8	42.6	4.9	61
	15.5	34.5	44.8	4.5	58
Fenamiphos	16.9	25.4	44.1	13.6	59
	4.5	27.3	50.0	18.2	44
Lindane	18.7	25.2	36.4	19.6	107
	20.2	26.3	32.3	21.2	99

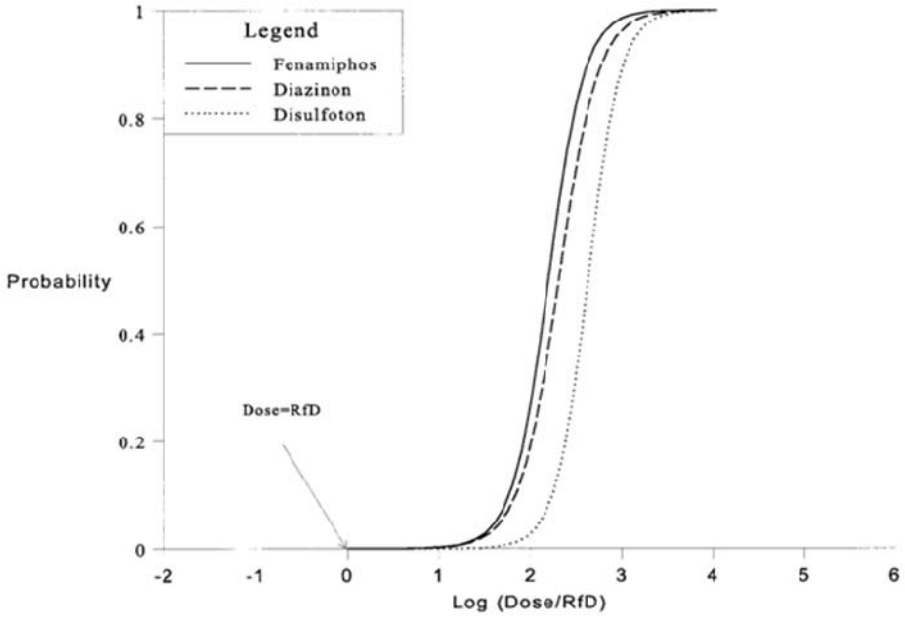
Teuschler, et al., 1999. Second line is censored data.

Probabilities in the next two graphs from Teuschler et al. (1999) indicate the likelihood that a toxicologist would judge the unknown dose group as an adverse or frank effect level in experimental animals, since the incoming data was based on experimental animal dose groups. An uncertainty factor for experimental animal to human is needed if the end result is to be this probability in humans. The interpretation of this human probability might be an estimate of the risk of the critical effect occurring in a sensitive subgroup. However, this interpretation does not specify the number of individuals responding, since the incoming data was based on dose groups.

Risk above the RfD for 2 Pesticides



Risk above the RfD for 3 Pesticides



References

Dourson, M.L., L.K. Teuschler, P.R. Durkin, and W.M. Stiteler. 1997. Categorical regression of toxicity data: a case study using aldicarb. Regul Toxicol Pharmacol. 25: 121-129.

Guth, D.J., Carroll, R.J., Simpson, D.G., Zhao, H., 1997. Categorical regression analysis of acture exposure to tetrachloroethylene. Risk Analysis 17: 321-332.

Hertzberg, R.C. and M.L. Dourson. 1993. Using categorical regression instead of a NOAEL to characterize a toxicologist's judgment in noncancer risk assessment. In: Proceedings, Second International Symposium on Uncertainty Modeling and Analysis, College Park, MD, B.M. Ayyub, ed. IEEE Computer Society Press, Los Alamitos, CA.: 254-261.

Meek, M.E., R. Newhook, R.G. Liteplo, and V.C. Armstrong. 1994. Approach to assessment of risk to human health for priority substances under the Canadian Environmental Protection Act. Environmental Carcinogenesis and Ecotoxicology Reviews. C12(2): 105-134.

Teuschler, L.K., M.L. Dourson, W.M. Stiteler, P. Mcclure, and H. Tully. 1999. Health risk above the reference dose for multiple chemicals. Regul Toxicol Pharmacol. 30: S19-S26.

U.S. Environmental Protection Agency. 2000. CatReg Software User Manual. National Center for Environmental Assessment. Research Triangle Park. EPA/600/R-98/052. Review Draft.

U.S. Environmental Protection Agency. 2002. A review of the Reference Dose (RfD) and Reference Concentration (RfC) processes. Risk Assessment Forum. EPA/630/P-02/002F, December.

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal for a Case Study

Your Name, affiliation, and e-mail:
Asish Mohapatra, Health Canada
Email: asish.mohapatra@hc-sc.gc.ca

1. Please identify the issue/problem formulation that the proposed method aims to address

Philosophical Basis:
To conduct investigation and analysis of heterogeneous data in problem formulation, dose-response assessment and exposure analysis in the evolutionary context of Science-Judgment--Risk Analysis" to "Science-Decisions-Risk Analysis. The existing and emerging Data Fusion methodologies would bridge the gap between Risk Assessment, Risk Management and Risk Communication in Environmental Public Health Risk Analysis.

Issues and Objectives:

Issues: To examine data fusion methodologies for toxicological dataset analysis to resolve data quality issues in predictive toxicology and to establish a collaborative computational toxicology and health risk analysis framework based on a dynamic data fusion model.

Objectives: The objective of a front end toxicological dataset integration via a dynamic knowledgebase and data fusion model would proactively detect patterns in toxicological datasets with the help of computational and informatics tools. Some of the emerging informatics tools (e.g., semantic web) can also be used to design a true collaborative platform. This component of the case study will be explored in future phases of the project. Fusion of various databases and the creation of a dynamic knowledgebase would then help next generation environmental health risk assessments to prevent environmental and human health consequences and protect public health. This approach helps provide a method for processing heterogeneous data (e.g., data sets at different organizational levels, such as 'omics and other data at the cellular level, organismic-level toxicity data, apical toxicity endpoints, population-level data, and data on exposure pathways).

2. Please describe the proposed method (1-3 pages). Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).

The proposed methodology is aimed at formulating a data fusion based modified Joint Director Laboratories (JDL) model that addresses heterogeneous datasets which can facililitate collaborative toxicological and health risk data integration and analysis The model is built around a set of algorithms in various levels of fusion (see figure 1), that can be executed continuously and autonomously in it's environment and able to carry out activities in a flexible and intelligent manner while being responsive to changes in it's environment. In a collaborative toxicology and health risk analysis platform, these changes can then be detected and recognized for further utilization in dose-response assessment and risk assessments. A detailed explanation of each level of fusion in the modified JDL model will be provided during the meeting.

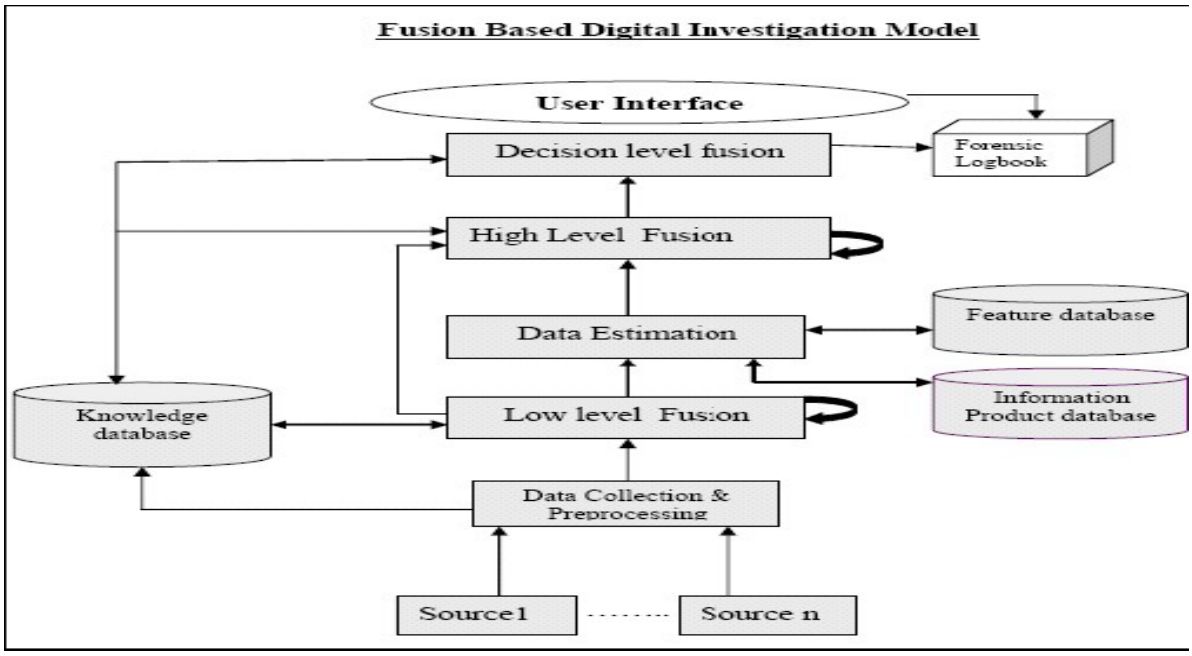


Figure 1: Data Fusion Based Investigation Model (A Modified JDL Model)

3. Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.

A case study is being proposed to evaluate a chemical or a list of chemicals (important from a contaminated sites risk assessment perspective) and prioritize them for further toxicological risk assessment evaluation.

Data Fusion Methods have been used in a wide range of applications (e.g., civil, military and non-military applications). Some of the environmental applications relate to real time dynamic data collection and processing (e.g., air pollution data, data from weather sensors, fate and transport of contaminants in the environment, etc.) and decisions are made to manage and communicate risks (if any). The modified JDL Model can be applied while evaluating heterogeneous datasets for a chemical toxicology review project (Table1). In this example, data are available on organism-level effects of the chemical, on exposure pathways, and on gene expression changes.

A Chemical Example (Table-1)

Chemical Toxicology-Exposure-Disease-Gene Dataset Fusion		
Chemical	**Disease Pathways**	**Genes**
Example: **A Petroleum Hydrocarbon Constituent** (This is just an example). Emerging Chemicals can be assessed and evaluated by using the modified JDL model.	Example: Pathways to Cancer Specific Exposure Datasets is can be mined from peer-reviewed literature (both laboratory and field datasets)	Inferred Gene Relationship – *BAX, BCL2 CASP3*

In light of emergence of datasets from computational toxicology efforts, stakeholders need to collaborate on toxicological data sharing and integration. These toxicogenomics (identification of toxicity and biological pathway) datasets are being generated for future public health risk assessment applications (Figure 2). The relationships between chemicals, exposure, diseases and genes can be effectively explored by chemical-genomics data fusion and further integrating them with exposure and disease databases.

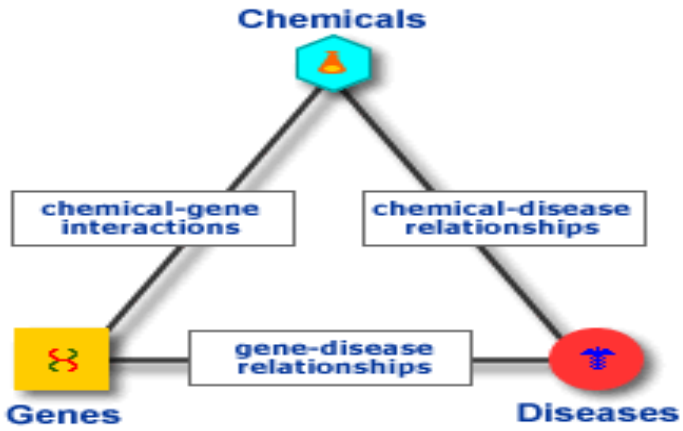


Figure 2: Chemical Disease and Genes Interactions and Relationships (Excerpted from Comparative Toxicogenomics Database, *with permission from The Comparative Toxicogenomics Database Group* (http://www.mdibl.org)

Our case study on data fusion methodologies and application in the context of a chemical or a list of chemicals would seek to evaluate how heterogeneous datasets for a specific chemical or a list of chemicals can be effectively fused and analyzed which would then help risk assessors and toxicologist in identifying issues and conducting dose-response analysis and exposure analysis from a public health perspective. Evaluation of various data fusion methodologies and in particular JDL model, key issues, gaps and opportunities can be identified and potential applications in emerging toxicological analytical methods under a regulatory risk assessment framework can be explored. This will lead to next generation of health risk assessments.

Under a regulatory framework, we not only deal with risk assessment issues but risk management and risk communication plays an equally important role in the assessment process in a dynamic manner. A Collaborative platform can be very effective in dynamically linking risk assessment, risk management and risk communication.

Potential Impacts in Toxicology and Health Risk Analysis:

Based on the broad objectives of NAS recommendations and to further refine toxicology and the risk assessment tools and processes (from a static to a more dynamic process), a data fusion and data mash up approach facilitated by emerging informatics tools can significantly increase the efficiency of dynamic data integration.

As indicated earlier, some of the emerging informatics tools (e.g., semantic web) can also be used to design a true collaborative platform. This component of the case study will be explored during the future phases of the project.

These collaborative tools and frameworks can then be used in both regional and global health risk analysis projects. Regionally, a specific chemical risk assessment or a contaminated sites risk assessment can be undertaken by integrating data from various sources and various levels of fusion (low, medium, and high and decision level fusion) would lead to robust risk assessments, effective risk management and efficient risk communication. Similarly, Global risk analysis projects such as global climate change, nanotechnologies and emerging Nanotoxicology, global food crisis and Chemical-Biological-Radiological and Nuclear (CBRN) risks can be effectively evaluated by integrating environmental, ecological, eco-system based, clinical, public health toxicology databases integration, mash-ups and fusion. These collaborative approaches would facilitate both intra- and inter-agency communication to assess, manage and communicate environmental and human health risks and bridge the gap between science, regulatory and policy professionals in toxicology and risk analysis.

4. Proposed team to develop case study:

- Asish Mohapatra, Chair of Toxicology-Applications, Reviews and Methodologies Working Group) and other members of the working group in Contaminated Sites Division, Health Canada. Discussions to take place in the fiscal year April 2010- April 2011.

- Technical assistance and discussions with computational toxicologists from *TERA* and other organizations are expected.

5. References:

A preliminary literature review has been completed. Some papers have been presented in some conferences and international proceedings. Some key references can be shared during the meeting.

Disclaimer: Information and views presented in this proposal represent the views of authors and not the organization that support the research. Any opinions, findings and conclusions or recommendations presented in the proposal and/or presentations at the meeting are those of authors and do not necessarily reflect the views and positions of Health Canada.

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:

Workshop Cochairs: Melvin Andersen, The Hamner Institutes for Health, MAndersen@thehamner.org; and Julian Preston, U.S. EPA, Preston.Julian@epamail.epa.gov.
Steering Committee Presenters: Robert Budinsky, Dow Chemical Company, RABudinsky@dow.com; and Michael Dourson, *TERA*, Dourson@tera.org.

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

   Central to the "Science and Decisions: Advancing Risk Assessment" framework is the nexus of risk assessment with problem formulation and risk management. A critical, quantitative element of the risk assessment is characterizing dose-response and the magnitude of the risk(s). From a biological perspective, the Human Relevance Framework's (HRF) Mode-of-Action (MOA) methodology provides a robust systematic, objective, and transparent approach for characterizing dose-response and the magnitude of the risk(s). The HRF methodology has evolved to include a "Key Event Dose-Response Framework (KEDRF) to further aid in conducting quantitative risk assessment. An excellent opportunity for applying both the HRF and KEDRF is in the area of nuclear-receptor-mediated toxicities since the underlying biology and key event outcomes have been described for a number of nuclear receptors. The current challenge is to couple the complex biology of nuclear receptors with classical endpoints of cell biology, pathology and the apical event (e.g., tumor development) and then apply statistical and dose modeling methods; biologists and statisticians must work together so that the most accurate dose-response model for quantifying and characterizing the magnitude of the risk can be achieved. In addition, instead of having to provide extensive mechanistic data for each nuclear receptor's MOA on a one-by-one basis, it would be beneficial to have a nuclear receptor MOA model for which common key events and dose-response models have been defined.

2. **Please describe the proposed method. Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   The current dose-response modeling of limited dose-response relationships for apical outcomes such as altered hepatic foci growth or liver tumor formation, is inadequate, especially for liver tumors induced by activation of nuclear receptors. With respect to CAR/PXR and PPARα, that belong to the 48 proteins comprising the nuclear receptor superfamily, or AHR, the only nuclear receptor that belongs to the 23 proteins in the PAS protein family, there are well-described biological concepts at work. These biological concepts include ligand-binding and activation of the receptor. Activation

includes a complex series of steps such as shedding of chaperon proteins, nuclear translocation, binding to partner proteins, binding to the DNA response element, recruitment of co-regulatory proteins, and all the downstream events involving mRNA processing. The ultimate signal from nuclear receptor-altered transcription are cellular signals that range from normal physiological response, adaptive responses as part of a stress response, more significant and sustained stress responses that can result in toxicity, and ultimately, histopathological changes that culminate in tumor promotion and tumor development. All of these steps can be describes in a series of dose-transitions and complex integrated dose-response modeling that links dose with key events and the apical outcomes. Dose-response modeling methods applied to nuclear receptor biology models would enable the development of a categorical Key Event Dose-Response Framework for nuclear receptors and facilitate an understanding of the critical dose-response data necessary to most accurately connect dose to risk. The utility of such a dose-response-key event model for nuclear receptor biology will facilitate how research and risk assessment can be conducted in the future as more and more pharmaceutical, natural compounds, and industrial chemicals are shown to produce both beneficial as well as adverse effects through nuclear receptor-mediated biology.

3. **Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

   Three nuclear receptors, AHR, CAR/PXR and PPARα, will be used as examples for how their biology linked to key events, classical measures of toxicology and histopathology can be used to define dose-response for liver tumors in rodents, including the goal of defining the most appropriate dose-response modeling for ligands for these receptors. The results of a nuclear-receptor/MOA workshop being planned for September 2010 will provide the basic scientific information and discussion around this example.

4. **Proposed team to develop case study (desired, but optional)**

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Proposal Submittal Form

Your Name, affiliation, and e-mail:
Michael Dourson
Toxicology Excellence for Risk Assessment (*TERA*)
dourson@tera.org

1. **Please identify the issue/problem formulation that the proposed method aims to address (e.g. Screening level assessment).**

   For the purposes of conducting a cost-benefit analysis, estimate the median and upper bound fraction of people expected to have an adverse noncancer effect at a specified exposure level.

2. **Please describe the proposed method (1-3 pages). Detailed descriptions are not needed, but sufficient information is needed to allow a preliminary evaluation of the utility of this method for the stated problem formulation (with references as needed).**

   This method is an extension of the benchmark dose (BMD) method that allows the development of risk values at doses above the Reference Dose (RfD) when the existing data are based on human responses. Although such examples are not numerous, when available the results can be quite credible.

   The appropriate BMD is chosen in the usual fashion using existing EPA software and criteria, including p-values, AIC, residuals, BMD to BMDL ratios and visual inspection. The data are modeled to an appropriate point of departure using the usual judgment, and then four different procedures are used to extrapolate the potential risk:

   - A straight line is drawn from both the BMDL and BMD to the RfD, where the RfD is considered to be zero risk;
   - The appropriate BMD model is extrapolated to the RfD and then the risk at the RfD is truncated to zero;
   - The appropriate BMD model is extrapolated to the RfD and this risk is allowed to stand as an upper bound;
   - The appropriate BMD model is extrapolated using a threshold term, where the threshold value is judged to be the RfD, or some higher value.

   All four procedures will be explored, and the problem formulation will be refined appropriately. For example, some methods may be more appropriate for screening-level estimates of risk, while others may be more appropriate for more comprehensive estimates.

3. **Please provide an example/case study which demonstrates how the method can be applied. The case study may be already completed, or a proposed application of the method.**

   The case study will use methyl mercury (MM). Several BMDs are available for MM for the critical effect in sensitive human populations, so that the usual extrapolation issues of average to sensitive human and experimental animal to human are mollified. Moreover, existing literature exists incorrectly implying that exposures above the RfD are with risk to a large population of sensitive humans. This is clearly not correct based on current understanding of the existing MM data and BMD estimates. The figure below shows a conceptual model representing all of these approaches, along with the cumulative frequency of blood Hg values in women from a recent NHANES study.

Proposed team to develop case study

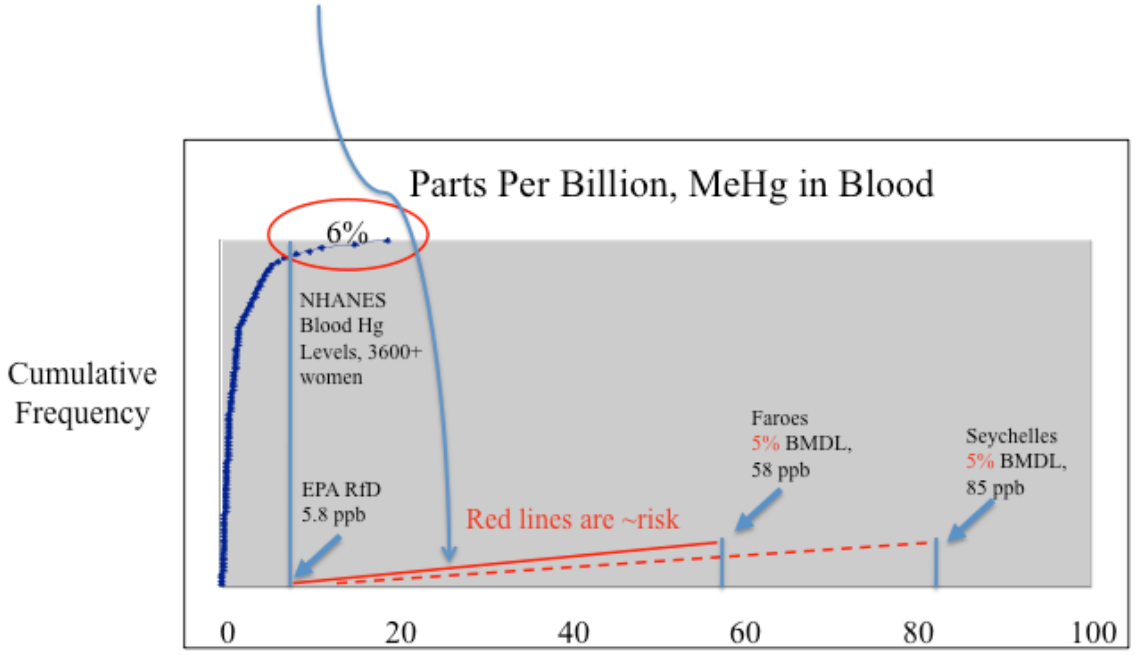
Michael Dourson, Toxicology Excellence for Risk Assessment
Rita Schoeny, U.S. Environmental Protection Agency
Tba: U.S. Environmental Protection Agency

References:

National Academy of Sciences. 2000. National Research Council. Toxicological effects of methylmercury. National Academy Press.

U.S. EPA (U.S. Environmental Protection Agency). 2010. Integrated Risk Information System (IRIS). National Center for Environmental Assessment. Online at www.epa.gov/iris.

Risk above EPA's Reference Dose



Source: EPA; NAS Toxicological Effects of Methylmercury (2000); EPA (2010).