Combining Data from Different Sources in Risk Assessment

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Outline

- Systematic review of available data
- Meta-analysis of summary risk estimates
- Combined analysis of primary raw data
- Categorical regression of toxicity severity scores
- Conclusions

Systematic Review

Critical Reviews in Toxicology

http://informahealthcare.com/txc
ISSN: 1040-8444 (print), 1547-6898 (electronic)

Crit Rev Toxicol, 2014; Early Online: 1–81
 DOI: 10.3109/10408444.2014.934439

informa
healthcare

REVIEW ARTICLE

Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts

Calvin C. Willhite[1,2], Nataliya A. Karyakina[1], Robert A. Yokel[3], Nagarajkumar Yenugadhati[2], Thomas M. Wisniewski[4], Ian M.F. Arnold[5], Franco Momoli[6,7,8], and Daniel Krewski[1,2,7]

Comprehensive and reproducible

Meta-analysis

A meta-analysis of observational studies of the association between chronic occupational exposure to lead and amyotrophic lateral sclerosis

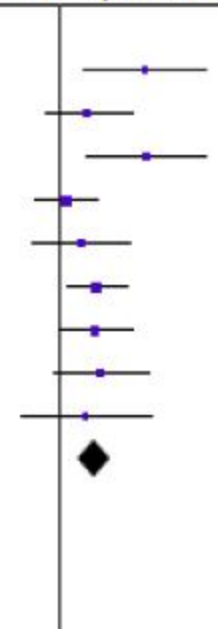
Ming-Dong Wang, PhD; James Gomes, PhD; Neil R. Cashman, MD; Julian Little, PhD; Daniel Krewski, PhD

(to appear in Journal of Occupational and Environmental Medicine, 2014)

Study or Subgroup	ALS Events	ALS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Exposure to Lead						
Armon1991	18	45	6	45	4.1%	4.33 [1.52, 12.34]
Campbell 1970	23	74	16	74	7.7%	1.63 [0.78, 3.43]
Chancellor 1993	19	103	5	103	4.2%	4.43 [1.59, 12.38]
Deapen 1986	30	518	27	518	13.3%	1.12 [0.65, 1.91]
Gresham 1986	16	66	12	66	6.1%	1.44 [0.62, 3.34]
Kamel 2002	35	102	53	246	14.4%	1.90 [1.14, 3.17]
McGuire 1997	21	174	24	348	10.5%	1.85 [1.00, 3.43]
Pierce-Ruhland 1981	20	80	11	78	6.5%	2.03 [0.90, 4.58]
Yu2014	9	66	6	66	3.7%	1.58 [0.53, 4.72]
Subtotal (95% CI)		**1228**		**1544**	**70.4%**	**1.81 [1.39, 2.36]**
Total events	191		160			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.25$, $df = 8$ ($P = 0.32$); $I^2 = 14\%$

Test for overall effect: $Z = 4.43$ ($P < 0.00001$)



Estimating the risks

Quality Scoring of Observational Studies

A Systematic Review and Meta-analysis of Childhood Leukemia and Parental Occupational Pesticide Exposure

Donald T. Wigle, Michelle C. Turner, and Daniel Krewski

McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada

Environmental Health Perspectives • VOLUME 117 | NUMBER 10 | October 2009

Quality scoring of cohort studies

Residential Pesticides and Childhood Leukemia: A Systematic Review and Meta-Analysis

Michelle C. Turner,[1,2] Donald T. Wigle,[1] and Daniel Krewski[1,3,4]

[1]McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, [2]Faculty of Graduate and Postgraduate Studies, and [3]Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada; [4]Risk Sciences International, Ottawa, Canada

Environmental Health Perspectives • VOLUME 118 | NUMBER 1 | January 2010

Quality scoring of case-control studies

Meta-analysis

OPEN ACCESS Freely available online

PLOS ONE

Intermediate CAG Repeat Expansion in the *ATXN2* Gene Is a Unique Genetic Risk Factor for ALS—A Systematic Review and Meta-Analysis of Observational Studies

Ming-Dong Wang[1]*, James Gomes[1], Neil R. Cashman[2], Julian Little[1]*, Daniel Krewski[1]*

1 Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, **2** Department of Medicine, University of British Columbia, Vancouver, Canada

Discovering new relationships

Systematic Review of Factors Affecting the Onset and Progression of Neurological Conditions

- ALS
- Alzheimer's disease
- Brain cancer
- Cerebral palsy
- Dystonia
- Epilepsy
- Huntingdon's disease
- Hydrocephalus
- Neurotrauma
- Multiple sclerosis
- Muscular dystrophies
- Parkinson's disease
- Spina biffeda
- Tourette's syndrome

Consider pre-existing systematic reviews to reduce the volume of work (with AMSTAR scoring)

Risk Factors Possibly Affecting the Onset of Priority Neurological Conditions

Biological	Genetic	Environmental/ Occupational	Lifestyle	Psychosocial/Social	Pharmacological	Demographic
Amyotrophic Lateral Sclerosis						
	• SOD1 monogenic mutation • C9ORF72 SOD1 monogenic mutation • ATAXIN 2	• Pesticides • Heavy metals such as lead • Organic solvents • Previous trauma • Electric shock				
Alzheimer's Disease						

Classify weight of evidence as sufficient , limited, or inadequate using simplified criteria

Systematic review summarizes the evidence, but does not necessarily weigh the evidence

Combined Analysis of Primary Raw Data

Residential Radon and Risk of Lung Cancer

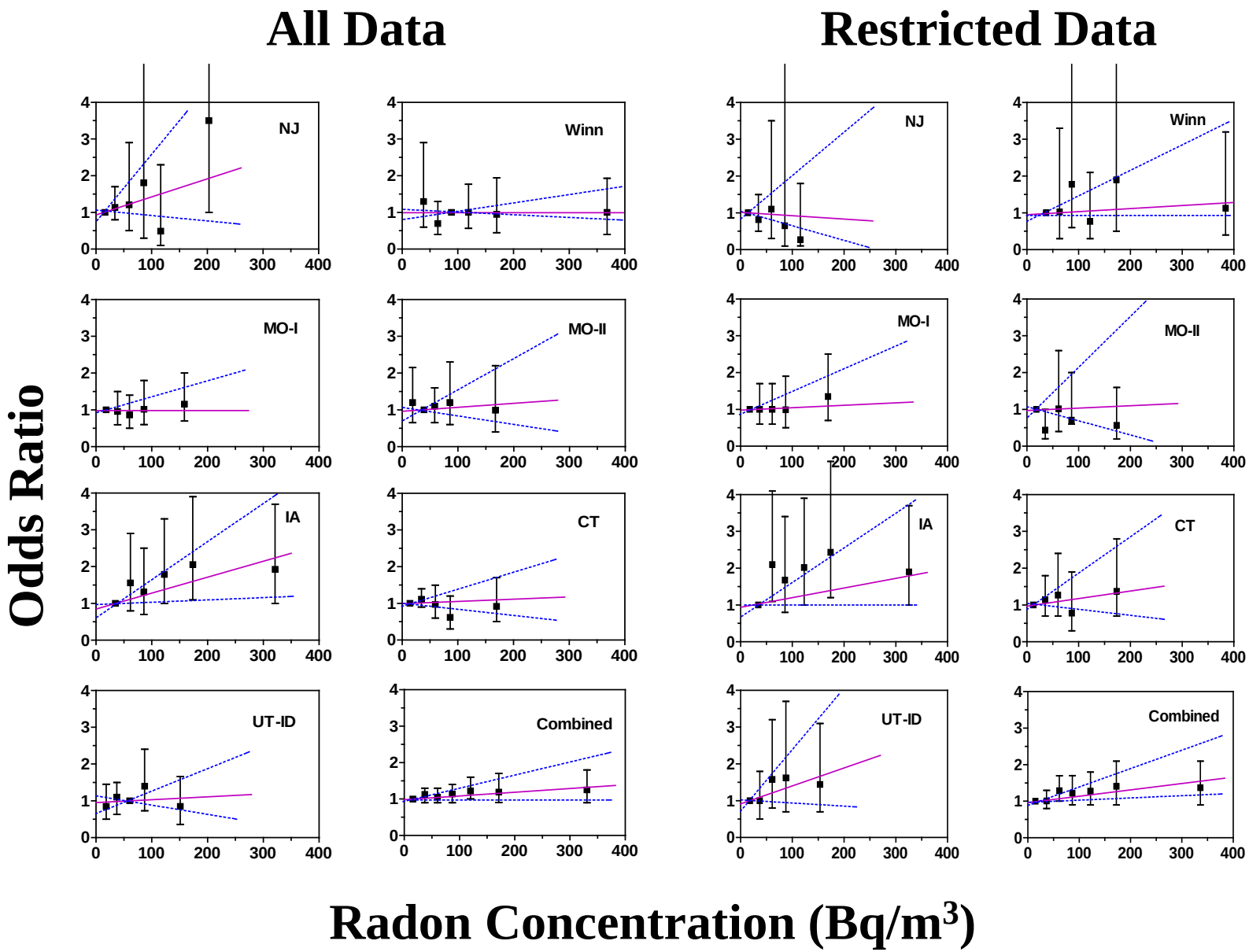
A Combined Analysis of 7 North American Case-Control Studies

Daniel Krewski,[*] Jay H. Lubin,[†] Jan M. Zielinski,[†] Michael Alavanja,[§] Vanessa S. Catalan,[‖] R. William Field,[*¶] Judith B. Klotz,[††] Ernest G. Létourneau,[‡‡] Charles F. Lynch,[¶] Joseph I. Lyon,[§§] Dale P. Sandler,[‖] Janet B. Schoenberg,[††] Daniel J. Steck,[¶¶] Jan A. Stolwijk,[***] Clarice Weinberg,[†††] and Homer B. Wilcox[††]*

Epidemiology • Volume 16, Number 2, March 2005

Explore modifying factors and heterogeneity

Exposure-response Curves for Individual and Combined Studies



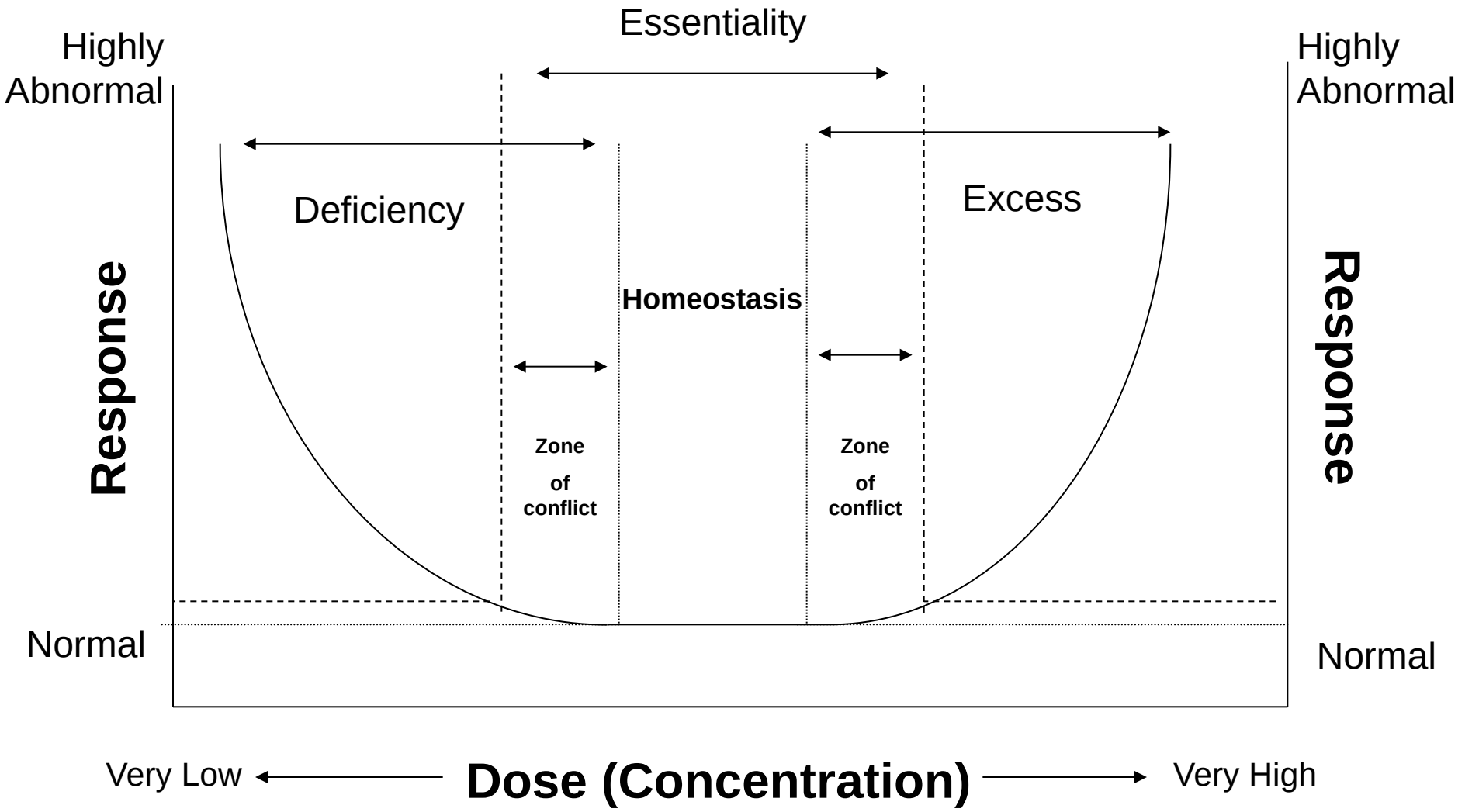
Categorical Regression

"An empirical modeling approach that involves the application of regression analysis and the organization of response data in the form of ordered categories of severity in order to predict the probability of achieving a particular severity category as a function of one or more independent variables (i.e., duration and concentration)."

- US EPA CatReg Manual

- Can be used to model *multiple studies and endpoints* simultaneously using a common toxicity metric

Dose-response relationships for essential trace elements are complex



Copper Dose-response Modeling: Phase I

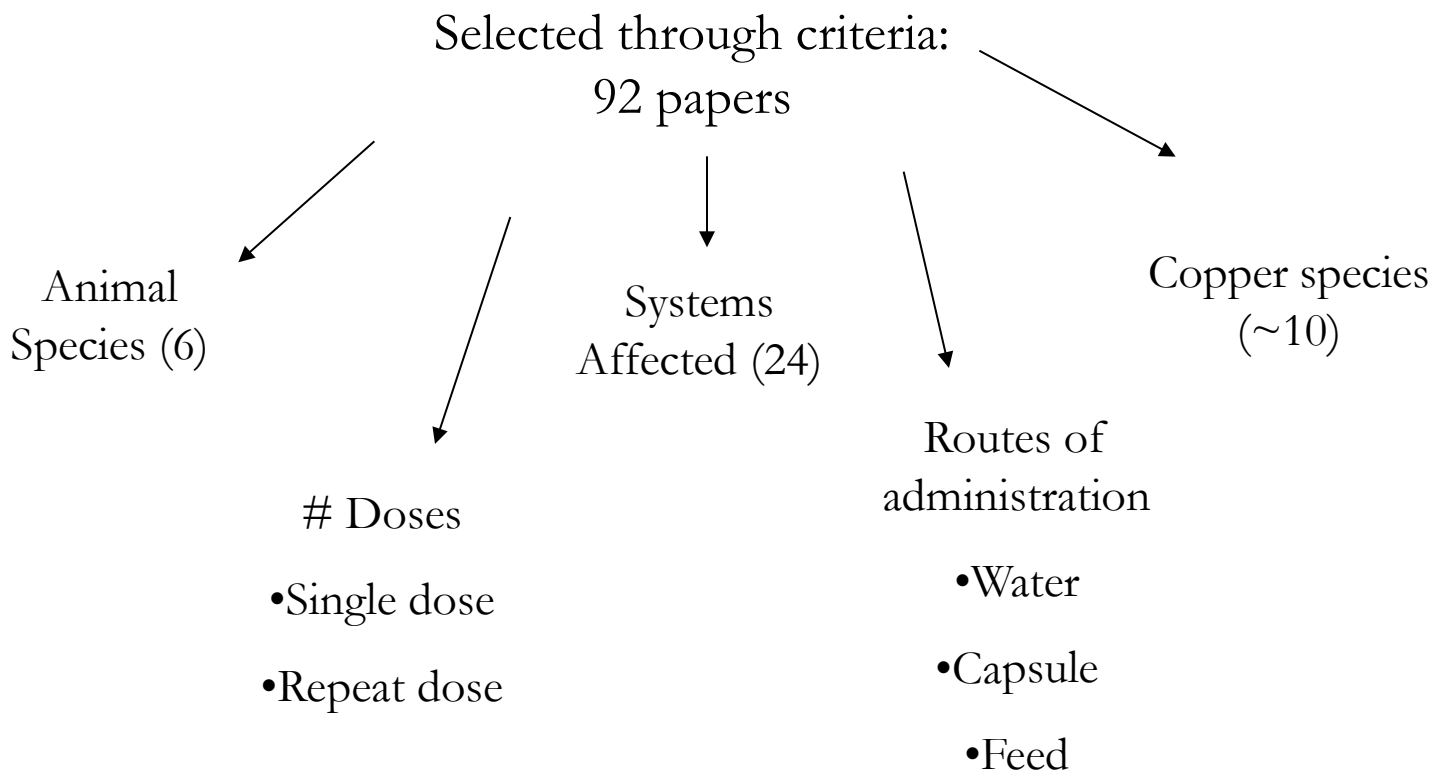
Copper Dose-response Working Group (2002)

Criteria Used for Exclusion of Studies

Most Useful ⟷ Least Useful				
1	2	3	4	5
Multiple dose or multiple outcomes from intact animals or humans Adequate Reporting Physiological Measures	Multiple or single dose from intact animals or humans Fairly Good Reporting Likely to yield useful information Change in time Points Cellular effects	Single dose or clinical study / case report with indeterminate dose Tracer or PK Study Info re. body burden or kinetics Mechanistic or cellular effects	No dose information Physiological information Review	No Utility

Selection of Studies
(Phase I: studies published through to 2002)

~600 Papers



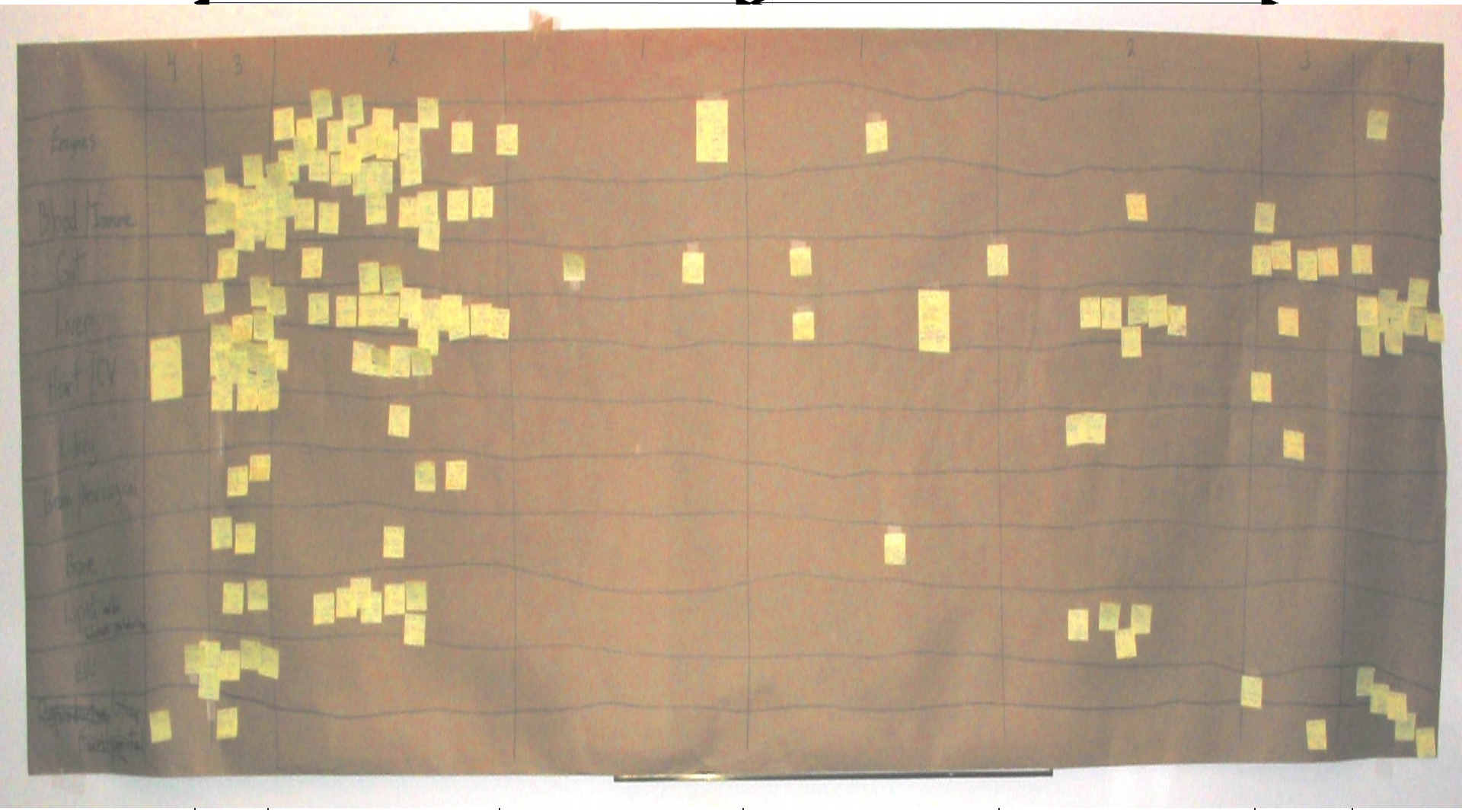
Severity Scoring

Deficiency Endpoints	Severity Score	Toxicity Endpoints
Cu burden; metallothionein; urine Cu	0	Cu burden; metallothionein; urine Cu
Loss of Cu-dependent enzyme function (SOD); Changed blood cell number or function	1	Changes in cholesterol and triglyceride levels in blood/liver; large Cu burden; body weight; nausea; diarrhea; enzyme changes without histopathology
Organ weight changes; plasma glucose/insulin; heart rate; EKG changes; minor histopatholgy; white blood cell activity/counts	2	Body weight; anemia; hemolysis; vitamin levels; liver enzymes; inflammation; organ weight changes
Mortality; gross histopathology reproductive function changes	3	Death; gross histopathology

Metabolic perturbations

Essentiality

Metabolic perturbations



Gross deficiency

Loss of Cu enzyme activity

Molecular manifestations

Molecular manifestations

Loss of Cu enzyme activity

Gross excess

Copper Toxicity Database (Phase I)

Journal of Toxicology and Environmental Health, Part A, 73:208–216, 2010

ISSN: 1528-7394 print / 1087-2620 online
DOI: 10.1080/15287390903340815

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DEVELOPMENT OF A COPPER DATABASE FOR EXPOSURE-RESPONSE ANALYSIS

Daniel Krewski[1], Andrea Chambers[1], Bonnie Ransom Stern[2], Peter J. Aggett[3], Laura Plunkett[4], Larisa Rudenko[5]

[1]McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada
[2]Consulting in Health Sciences and Risk Assessment, BR Stern and Associates, LLC, Annandale, Virginia, USA
[3]Emeritus Professor, Parbold, United Kingdom
[4]Integrative Biostrategies, LLC, Houston, Texas, USA
[5]Integrative Biostrategies, LLC, Washington, DC, USA

Copper Toxicity Database (Phase I): Number of Observations by Species and Severity Level

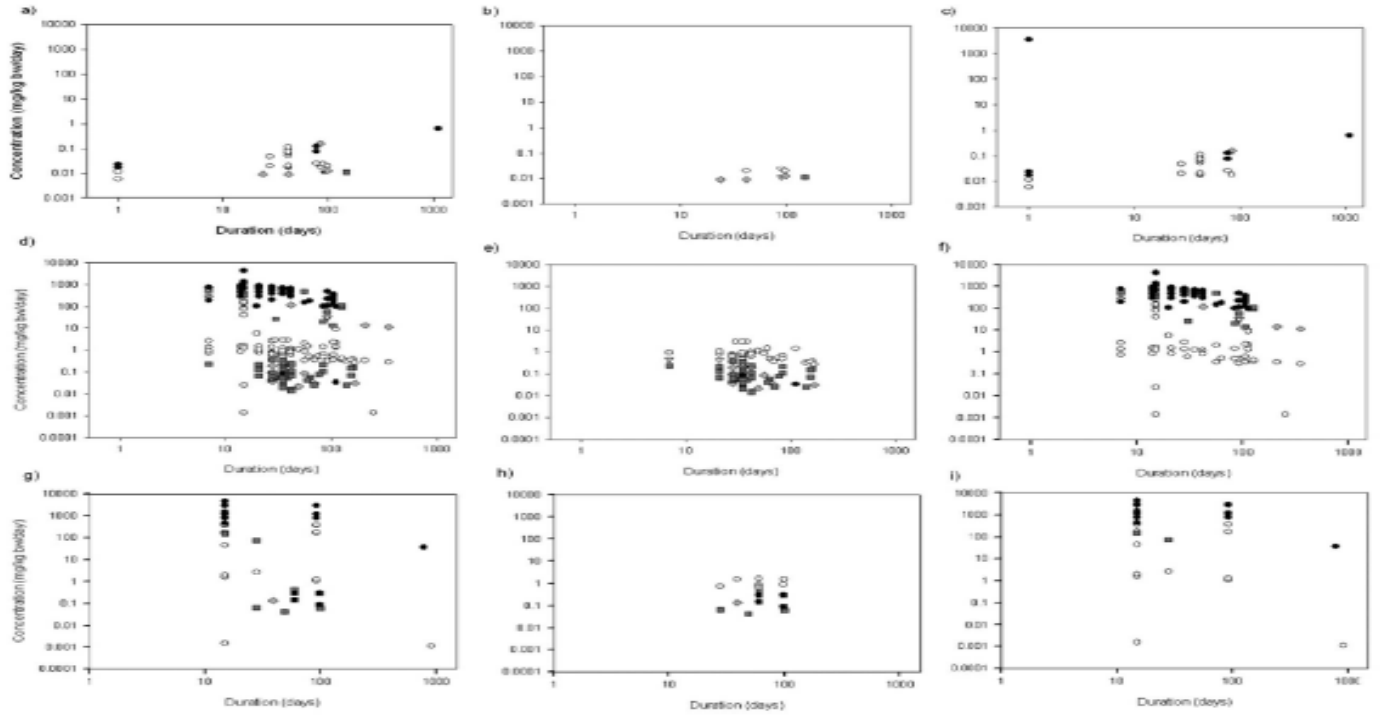
Factor	Number of observations	
	Deficiency	Excess
Severity level		
0	59	83
1	5	6
2	18	4
3	48	16
4	6	76
Animal species		
Humans	8	22
Rats	108	117
Mice	18	40
Pigs	2	6

Copper Toxicity Database (Phase I): Data Displayed by Excess/Deficiency, Species, and Severity

Deficiency/Excess

Deficiency

Excess



Humans

Rats

Mice

FIGURE 2. Copper excess and deficiency data, copper deficiency data and copper excess data on humans (a–c), rats (d–f), and mice (g–i), respectively. Concentration is defined in mg/kg bw/d and duration is defined in days. Data points are represented as: ○ – severity level 0, ▽ – severity level 1, ◇ – severity level 2, ■ – severity level 3, ● – severity level 4.

Copper Dose-response Modeling (Phase I)

Journal of Toxicology and Environmental Health, Part A, 73: 1–15, 2010

ISSN: 1528-7394 print / 1087-2620 online
DOI: 10.1080/15287390903340781

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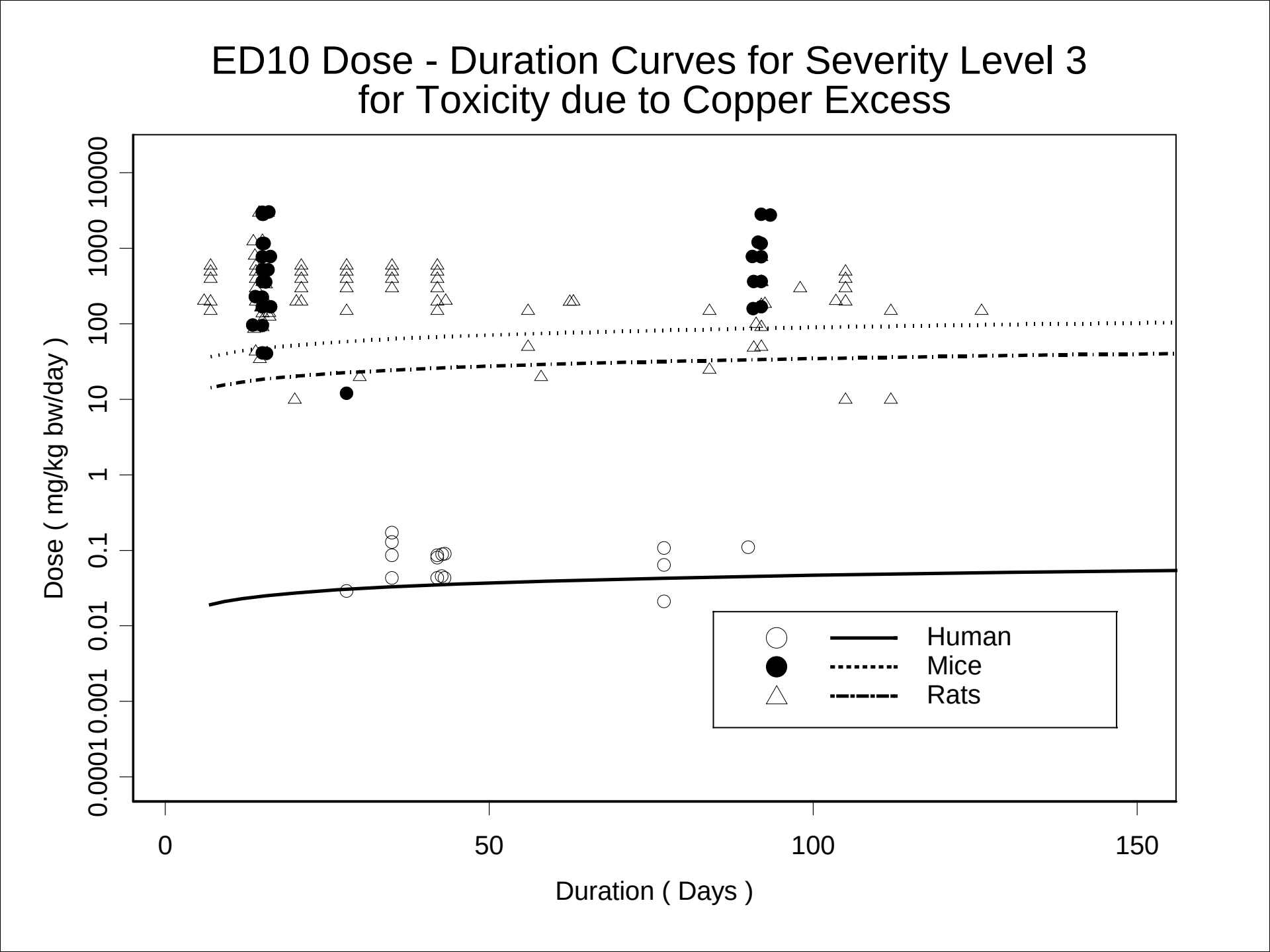
The Use of Categorical Regression in Modeling Copper Dose-Response Relationships

Daniel Krewski[1], Andrea Chambers[1], and Nicholas Birkett[2]
[1]*McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Ontario, and* [2]*McLaughlin Centre for Population Health Risk Assessment and Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada*


ED10 Dose - Duration Curves for Severity Level 3
for Toxicity due to Copper Excess
Dose (mg/kg bw/day)
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
0
50
100
150
Duration (Days)
Human
Mice
Rats

Interspecies Scaling

- Interspecies scaling based on four dose metrics:

Body weight:	mg/kg bw/day
Surface area:	$bw^{2/3}$
Intermediate:	$bw^{3/4}$ *(Travis & White, 1988)*
Total intake:	mg/day

Copper Dose-response Modeling: Phase II

Copper Dose-response Working Group (2009)

	Severity Score	Response
Copper Excess	6	Death
	5	Irreversible Gross Excess
	4	Reversible Gross Excess
	3	Metabolic Perturbation
	2	Early Biological Indicators Altered Cu Metabolism
AROI	1	Homeostatic Adaptation to High Intakes
No Effect	0	No change compare to controls
	0	
	1	Homeostatic Adaptations to Low Intakes
Copper Deficiency	2	Early Biological Indicators of Def Cu Levels
	3	Metabolic Perturbation
	4	Reversible Gross Deficiency
	5	Irreversible Gross Deficiency
	6	Death

Journal of Toxicology and Environmental Health, Part B, 13:546–578, 2010

ISSN: 1093-7404 print / 1521-6950 online
DOI: 10.1080/10937404.2010.538657

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AN EXPOSURE-RESPONSE CURVE FOR COPPER EXCESS AND DEFICIENCY

Andrea Chambers[1], Daniel Krewski[1], Nicholas Birkett[1,2], Laura Plunkett[3], Richard Hertzberg[4], Ruth Danzeisen[5], Peter J. Aggett[6], Thomas B. Starr[7], Scott Baker[5], Michael Dourson[8], Paul Jones[9], Carl L. Keen[10], Bette Meek[11], Rita Schoeny[12], Wout Slob[13]

Number of Observations by Species and Severity Score

	Severity Levels						
Factor	*0*	*1*	*2*	*3*	*4*	*5*	*6*
Copper Excess							
Humans	12 (28)	**0**	4 (5)	0	6 (13)	0	0
Rats	7 (55)	0 (8)	0 (3)	2 (17)	4 (46)	0 (3)	0 (4)
Mice	2 (21)	0	0	2 (4)	0 (14)	0	0 (5)
Pigs	8 (8)	0	3 (3)	3 (3)	0	0	0
Rabbits	1 (1)	0	0	1 (1)	0	0	0
Copper Deficiency							
Humans	2 (5)	2 (3)	0 (3)	**1** (2)	0	0	0
Rats	27 (74)	6 (10)	6 (22)	21 (64)	**5** (6)	0	0 (1)
Mice	2 (11)	6 (0)	0 (1)	2 (2)	0 (4)	0	0
Pigs	0 (1)	0	0	0 (1)	0	0	0

* Bolded values represent the number of observations added from the literature review update and values in parenthesise represent the total number of observations including those identified prior to 2002.

Goodness of Fit
Under Alternative Model Specifications

TABLE 5. AIC for 24 Modeling Options for Copper Excess and Deficiency

Link Function	C	T	AIC	
			Deficiency	Excess
Logit	Linear	Linear	514.3146	576.76
Logit	Linear	Log	511. 2093	574.78
Logit	Log	Linear	514.3866	547.11
Logit	Log	Log	511.1258	541.52
Probit	Linear	Linear	518.7908	579.49
Probit	Linear	Log	517.7919	579.79
Probit	Log	Linear	518.8718	574.04
Probit	Log	Log	517.8761	543.70
C Log-log	Linear	Linear	514.5548	NA*
C Log-log	Linear	Log	505.7347	NA*
C Log-log	Log	Linear	514.6525	NA*
C Log-log	Log	Log	505.8695	NA*

Model Stratification Options (Species, Exposure Medium, Age)

TABLE 6. Stratification Options in the Cumulative Odds Model for the Copper Excess and Copper Deficiency Data

Stratification Option	Chi-square	df	P-value
Copper Excess:			
Intercept Stratified by Animal Species[a]	20.98	4	<0.05
Intercept Stratified by Exposure Medium[b]	7.07	3	<0.05
Concentration Stratified by Animal Species[c]	8.07	3	<0.05
Concentration Stratified by Age[b]	11.40	2	<0.05
Copper Deficiency:			
Intercept Stratified by Animal Species[c]	83.62	3	<0.0001
Intercept Stratified by Age[b]	11.93	2	<0.01

Cumulative Odds Model for Copper Excess

TABLE 7. Parameter Estimates, Standard Errors, Z-test Statistics and P-values for Copper Excess Studies Using the Cumulative Odds Model*

Parameter	*Estimate*	*Std. Error*	*Z-test*	*P-value*
SEV1	5.8797	3.1609	1.8601	0.0629
SEV2	5.4416	3.2080	1.6963	0.0898
SEV3	5.0383	3.2206	1.5644	0.1177
SEV4	4.0248	3.2062	1.2553	0.2094
HU:F:INTERCEPT	0.0000	0.0000	NA	NA
HU:W:INTERCEPT	1.9743	1.2831	1.5387	0.1239
MU:F:INTERCEPT	-19.1012	7.6620	-2.4930	0.0127
MU:W:INTERCEPT	-15.6647	5.9865	-2.6167	0.0089
RT:F:INTERCEPT	-13.8327	3.1243	-4.4274	<0.0001
RT:W:INTERCEPT	-12.9416	3.2232	-4.0152	<0.0001
HU:2:LG10CONC	9.7482	2.8460	3.4252	0.006
MU:1:LG10CONC	5.8122	3.7392	1.5544	0.1201
MU:2:LG10CONC	3.8369	2.4670	1.5537	0.1203
RT:1:LG10CONC	3.2419	0.4016	8.0731	<0.0001
RT:2:LG10CONC	2.4122	0.3361	7.17777	<0.0001
LG10TIME	2.5437	0.6976	3.6463	<0.001

* Cumulative odds model uses the logit link function. Concentration (mg/kg bw/days) and duration (days) have been log transformed to the base 10.
Note. SEV, severity level; LG10, log transformed to the base 10; CONC, concentration coefficient; TIME, duration coefficient; HU, humans; RT, rats; MU, mice; F, dietary studies; W, drinking water studies; 1, young animal (≤30 days of age); 2, mature animal (>30 days of age for rodents and ≥18 years for humans).

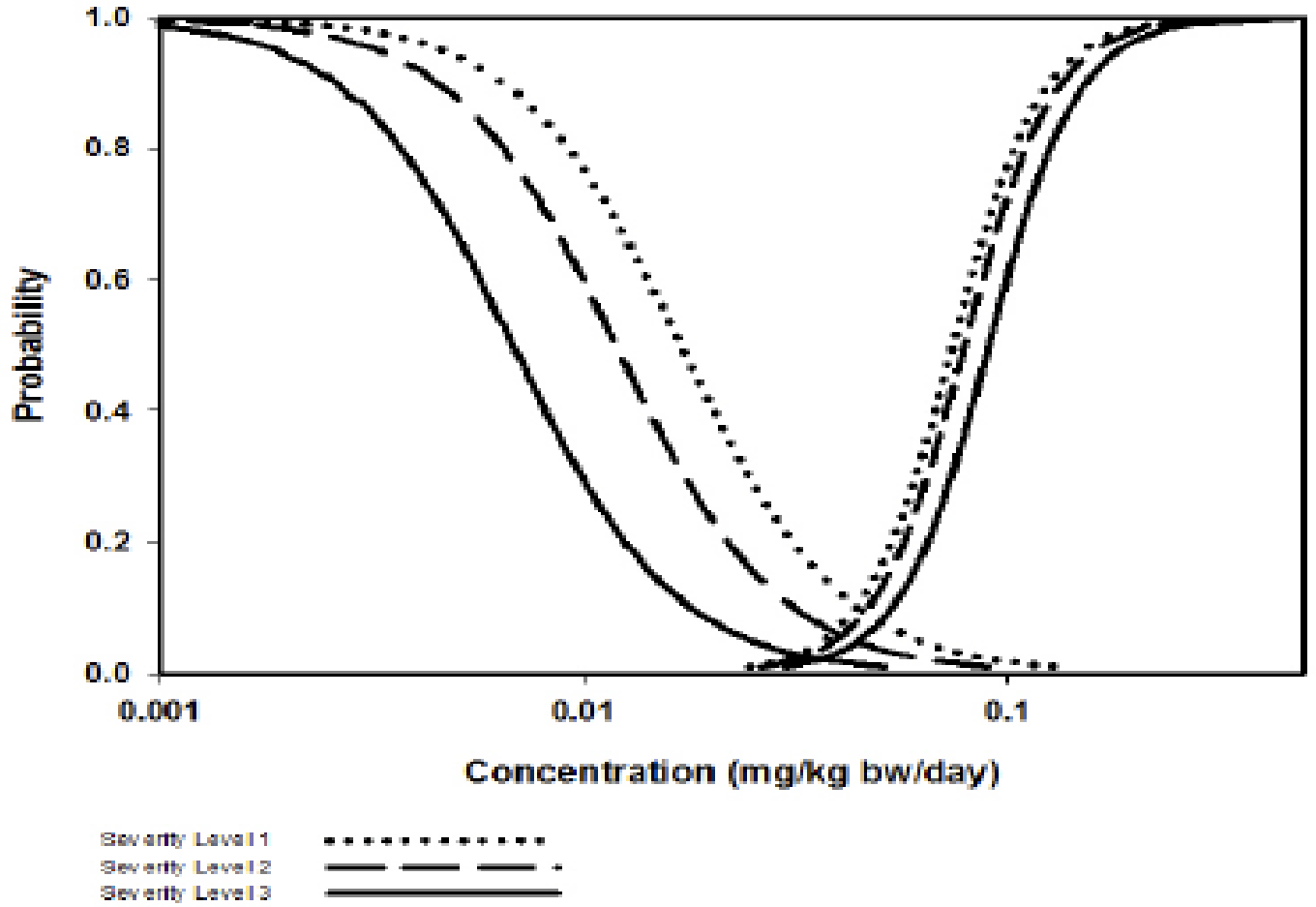
Cumulative Odds Model for Copper Deficiency

TABLE 8. Parameter Estimates, Standard Errors, Z-test Statistics and P-values for the Cumulative Odds Model* of the Copper Deficiency Data

Parameter	*Estimate*	*Std. Error*	*Z-test*	*P-value*
SEV1	-9.7115	1.7215	-5.6414	<0.0001
SEV2	-10.5141	1.7354	-6.0585	<0.0001
SEV3	-11.7843	1.7663	-6.6720	<0.0001
SEV4	-15.8934	1.9502	-8.1498	<0.0001
HU:2:INTERCEPT	0.0000	0.0000	NA	NA
MU:1:INTERCEPT	9.2461	1.7256	5.3583	<0.0001
MU:2:INTERCEPT	7.6482	1.0245	7.4655	<0.0001
RT:1:INTERCEPT	6.7146	0.7683	8.7391	<0.0001
RT:2:INTERCEPT	4.6963	0.6322	7.4285	<0.0001
LG10CONC	-5.2314	0.5517	-9.4817	<0.0001
LG10TIME	0.2247	0.9321	0.2410	0.8095

* Cumulative odds model uses the logit link function. Concentration (mg/kg bw/day) and duration (days) log transformed (log10). Note. SEV, severity level; LG10, log transformed to the base 10; CONC, concentration coefficient; TIME, duration coefficient; HU, humans; MU, mice; RT, rats; 2, mature animals (>30 days of age) or adult humans (≥18 years of age); 1 = young animals (≤30 days of age).

Dose-Response Curves for Copper Deficiency and Excess



Optimal Intake of Copper

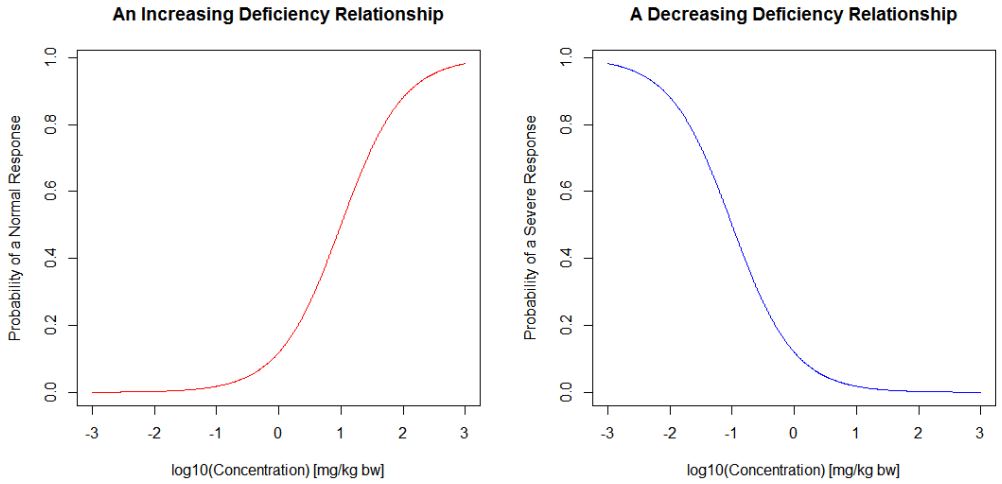
Using this model, an optimal intake level of 2.6 mg Cu/day was determined. This value is higher than the current US recommended dietary intake (RDI; 0.9 mg/day) that protects against toxicity from copper deficiency. It is also lower than the current tolerable upper intake level (UL; 10 mg/day) that protects against toxicity from copper excess.

Chambers et al. (2010)

Extended Copper Dose-response Modeling

- *CatReg* was designed to model increasing relationships

- To model deficiency, it is necessary to impose an increasing relationship



- It is not possible to model excess and deficiency simultaneously

A New Approach to Modeling U-shaped Curves

A Joint Model for Excess and Deficiency (JMED)

Assuming the response variable has been dichotomized, the JMED is defined to capture dose concentration and origin of toxicity in one well-defined model.

Define

$$x_{i1} = log_{10} \text{ concentration of the } i^{th} \text{ observation}$$

$$x_{i2} = \begin{cases} 1, & excess \\ 0, & deficiency \end{cases}$$

The JMED model is expressed as:

$$logit[P(Y_i = 1)] = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i1} x_{i2}$$

JMED Components

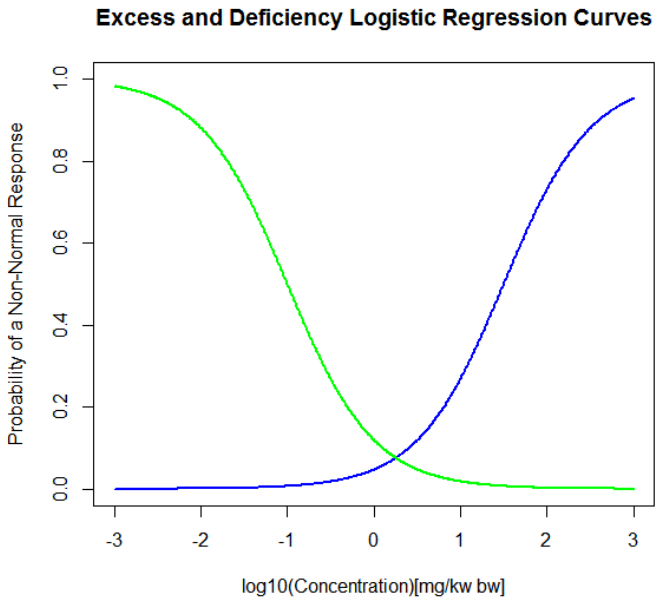
The JMED is comprised of excess and deficiency components.

The log odds of a non-normal response for deficiency and excess, respectively, are:

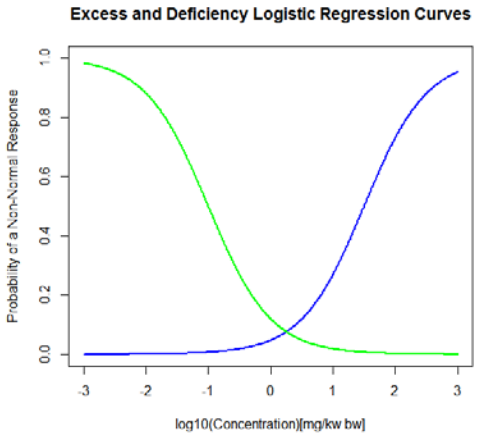
$$logit[P_D(Y_i = 1)] = \beta_0 + \beta_1 x_{i1}$$

$$logit[P_E(Y_i = 1)] = \beta_0 + \beta_2 + (\beta_1 + \beta_3) x_{i1}$$

Assuming $\beta_1 < 0$, $\beta_3 > 0$, and $\beta_1 + \beta_3 > 0$, a display of $logit[P_D(Y_i = 1)]$ and $logit[P_E(Y_i = 1)]$ versus x_{i1} would appear as:



Investigating the Point of Intersection



The intersection point between the excess and deficiency curves has been named the ***equiprobable crossover point*** *(EPCP).*

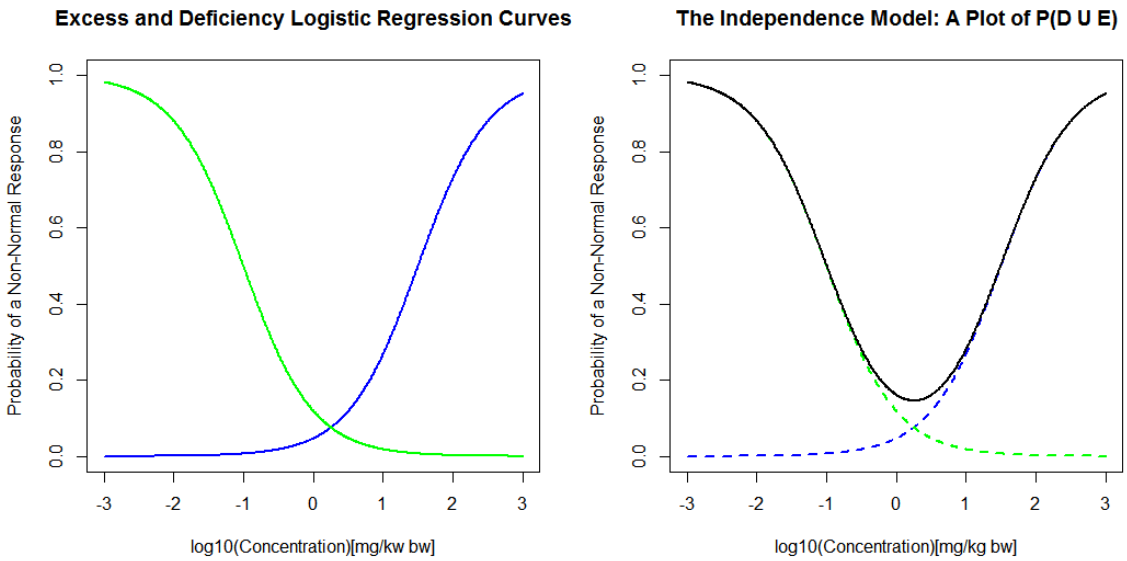
It is possible to obtain a closed form solution for the EPCP by equating $logit[P_D(Y_i = 1)]$ and $logit[P_E(Y_i = 1)]$, and solving for x_{i1}.

$$EPCP = -\frac{\beta_2}{\beta_3}$$

The EPCP represents the concentration level where the probability of excess is equivalent to the probability of deficiency.

The Independence Model

In addition to the EPCP, a second quantity of interest is the probability of excess or deficiency, or both.

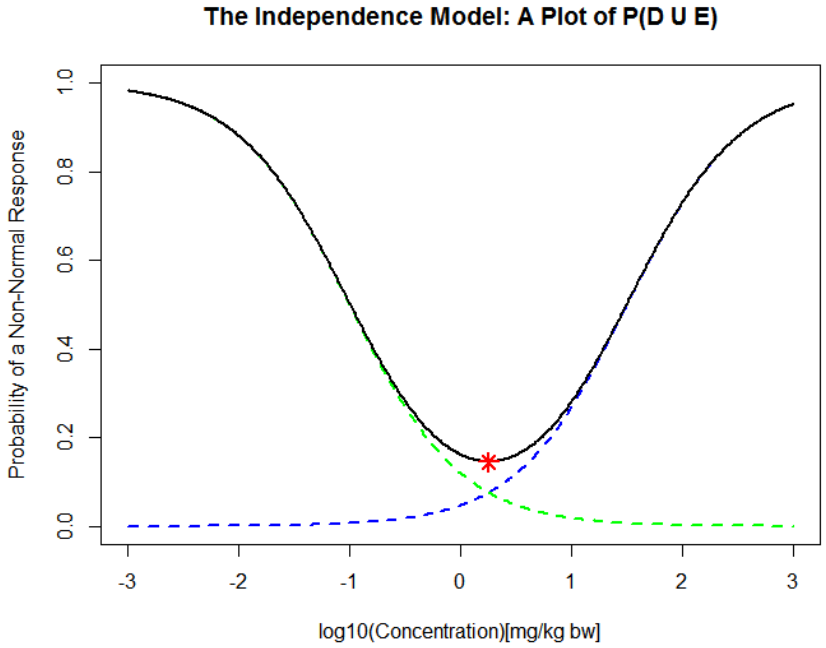


The Independence Model is expressed as:

$$P_{DUE}(Y_i = 1) = P_D(Y_i = 1) + P_E(Y_i = 1) - P_D(Y_i = 1)\, P_E(Y_i = 1)$$

The Independence Model: Investigating x_{MINDUE}

x_{MINDUE} represents the dose that will minimize the probability of a departure from a normal reading.



There is no closed form solution for xMINDUE → Solve numerically using Newton's Method

Application of the JMED to Copper

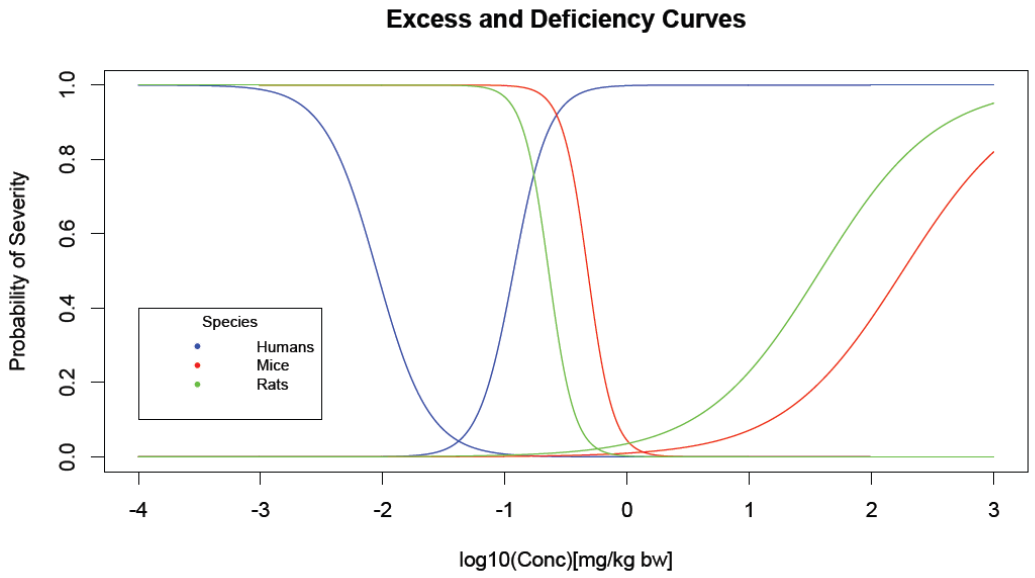
- The inclusion of indicator variables for rats and mice facilitates a species-specific analysis where humans are considered the baseline
- Results developed for the general case EPCP and x_{MINDUE} will readily extend

$$x_{i3} = \begin{cases} 1, & if\ mouse \\ 0, & otherwise \end{cases} \qquad x_{i4} = \begin{cases} 1, & if\ rat \\ 0, & otherwise \end{cases}$$

- Define

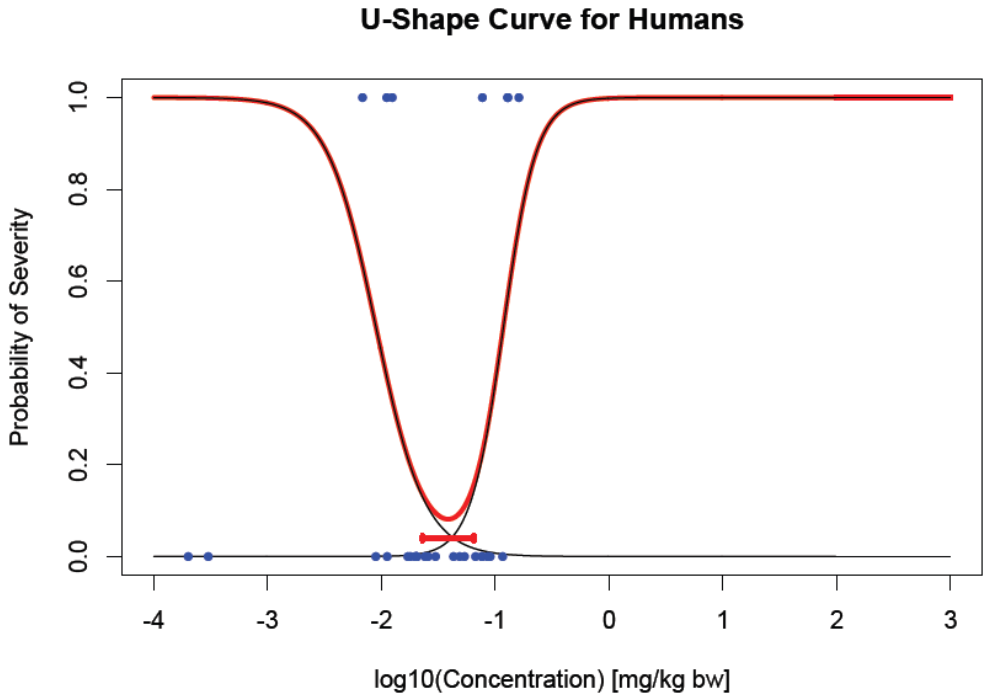
$$P(Y_i = 1) = \frac{\exp\left(\sum_{k=0}^{9} x_{ik}\beta_k\right)}{1+\exp\left(\sum_{k=0}^{9} x_{ik}\beta_k\right)}$$

The species-stratified JMED is :



Optimal Intake of Copper

X_{MINDUE} = 2.73 mg/day



For humans, a daily oral intake of **2.73 mg** will minimize the probability of a departure from a non-normal response attributed to excess or deficiency. The 95% confidence interval for X_{MINDUE} is (1.57, 4.46) and is analogous to an acceptable range of oral intakes.

Conclusions

- Systematic review useful in summarizing the available evidence to support both hazard identification and risk estimation
- The results of the systematic review still needs to evaluated with respect to both quality and weight of evidence for causality
- Meta-analysis and combined analysis useful for obtaining an overall summary measure of risk, based on good quality available data
- Categorical regression provides an approach to combining data from multiple studies on diverse endpoints in different test systems

Possible New Paradigm for QRA:

SR + *MA/CA/CR* = *Unit risk*

Summarize the evidence	Quantify the evidence	Best possible overall estimate of risk