Attachment 4-5

Guidance for Developing Ecological Soil Screening Levels (Eco-SSLs)

Eco-SSL Standard Operating Procedure (SOP) # 6: Derivation of Wildlife Toxicity Reference Value (TRV)

OSWER Directive 92857-55

November 2003

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Attachment 4-5

Ecological Soil Screening Levels (Eco-SSLs) Standard Operating Procedure (SOP) #4: Derivation of Wildlife Toxicity Reference Value (TRV)

OSWER Directive 92857-55

November 2003

Prepared for USEPA Region 8

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1.0 INTRODUCTION

The United States Environmental Protection Agency (USEPA) Office of Emergency and Remedial Response (OERR) with the assistance of a multi-stakeholder workgroup developed risk-based ecological soil screening levels (Eco-SSLs). Eco-SSLs are concentrations of contaminants in soils protective of ecological receptors that commonly come into contact with soil or ingest biota that live in, or on soil. Eco-SSLs are derived separately for four groups of ecological receptors: plants, soil invertebrates, birds and mammals.

Plant and soil invertebrate Eco-SSLs are developed from available plant and soil invertebrate toxicity data. The mammalian and avian Eco-SSLs are the result of back-calculations from a Hazard Quotient (HQ) of 1.0. The HQ is equal to the dose (associated with the contaminant concentration in soil) divided by a toxicity reference value (TRV). Generic food chain models are used to estimate the relationship between the concentration of the contaminant in soil and the dose for the receptor (mg/kg body weight/day). The TRV represents a numerical estimate of a no observable adverse effect level (dose) for the respective contaminant primarily for the endponts of growth, reproduction and survival.

The procedure(s) for deriving the mammalian and avian oral TRVs for calculation of Eco-SSLs are contained within four standard operating procedures (SOPs):

- Eco-SSL SOP #3 Wildlife TRV Literature Search and Retrieval (Attachment 4-2)
- Eco-SSL SOP #4 Wildlife TRV Literature Review, Data Extraction and Coding (Attachment 4-3)
- Eco- SSL SOP #5 Wildlife TRV Data Evaluation (Attachment 4-4)
- Eco-SSL SOP #6 Derivation of the Oral TRV (Attachment 4-5)

This document serves as SOP #6 and describes the procedure for derivation of the wildlife TRVs.

1.1 Purpose

The purpose of the SOP is to provide a clear written description of the procedures for derivation of the wildlife TRVs used for the calculation of the Eco-SSLs. The document is written with two primary objectives:

1) To allow the users of the Eco-SSL values to fully understand how the wildlife TRVs are derived including the basis for any assumptions used in the derivation process.

2) To allow users of the guidance to derive wildlife TRVs for additional contaminants for

which Eco-SSLs are not available at this time. This provides for reproducible and consistent results.

1.2 Scope

The second section of this SOP discusses how the results from the preceding SOPs (literature search, data extraction and data evaluation) are to be presented. Section 3 describes the process for plotting the toxicological data (NOAEL and LOAEL values). Section 4 describes the process for derivation of the wildlife TRV based on the results of Sections 2 and 3. Section 5 provides references.

This SOP is written as the fourth part of the wildlife TRV derivation process and it is assumed that the reader is familiar with the preceding three portions of the process. Some results are used in this SOP for illustration purposes.

Wildlife TRV Derivation Process

The wildlife TRV derivation process is composed of four general steps:

- **Literature Search and Retrieval**
  Eco-SSL SOP #3: Wildlife Literature Search and Retrieval (Attachment 4-2) . A literature search identifies dose-response literature for retrieval.

- **Literature Review and Data Extraction**
  Eco-SSL SOP#4: Wildlife TRV Literature Review, Data Extraction and Coding (Attachment 4-3).
  The retrieved literature studies are reviewed and data are extracted according to an established coding system. Data are entered into an electronic data base

- **Data Evaluation**
  Eco-SSL SOP#5: Wildlife TRV Data Evaluation (Attachment 4-3). Each of the results identified in the reviewed literature is scored for quality and applicability for TRV derivation.

- **TRV Derivation**
  Eco-SSL SOP#5: Wildlife TRV Derivation (Attachment 4-5). This procedure plots the collective dose-response information and establishes the process for estimating the TRV.

2.0 PRESENTATION AND REVIEW OF THE TOXICOLOGICAL DATA

2.1 Reporting the Results of the Literature Search

The literature search and review results for each contaminant are reported as three separate categories:

1) Literature from which useful toxicological data is identified and extracted (literature coded);

2) Literature rejected for use; and,

3) Literature that is pending review.

Each of the citations on these lists are identified with a unique record number assigned as part of the data extraction process as described in Attachment 4-3. Citations on the "literature rejected" list are labeled with respective literature rejection criteria as described in Attachment 4-3.

2.2 Reporting the Results of Data Review and Evaluation

An electronic database was created to facilitate efficient and accurate data extraction from individual reviewed toxicological studies. This database is fully described as Attachment 4-3. Extraction of the data directly into an electronic database facilitates the necessary sorting, searching and presentation of the data for the purposes of TRV derivation. A web-based data entry system is used allowing remote access by multiple reviewers from any computer with Internet capabilities. Entry to the site is password-protected and limited to only those individuals responsible for data entry and quality assurance. All information entered is sent directly to the master database (housed with the ECOTOX database by the EPA Office of Research and Development (ORD) National Health and Ecological Effects Research Laboratory (NHEERL), Mid-Continent Ecology Division-Duluth (MED-Duluth)) avoiding any quality assurance problems associated with merging multiple sources of information into one database. The web-based system provides for immediate access to the entered data with any changes to the database or data entry process being immediately reflected on the website.

The coding guidelines used for the Eco-SSL Wildlife TRV effort follow the same basic structure as that used by EPA Duluth for ECOTOX. There are, however, some necessary additions and exclusions from the TRV coding system. The TRV database is focused on extracting the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) doses from each of the toxicological studies while the TERRETOX system is designed to record all toxicological results from the studies.

2.3 Organizing and Presenting the Data and Data Evaluation Scores

The toxicity data is downloaded from the database into excel spreadsheet files for each contaminant using the tabular format provided in Table 2.1. One table is constructed for avian data and a second for mammalian data. The tables provide the essential information concerning each of the toxicity testing results. Table 2.1 provides an example of the output for mammals and cobalt. The results are numbered sequentially and then sorted by general effect group, effect type and effect measure.

Table 2-1 Example of Mammalian Toxicity Data Extracted and Reviewed for Wildlife Toxicity Reference Value (TRV)

Ref		Exposure														Effects						Conversion to mg/kg bw/day Dose							Result		Data Evaluation Score											
Result #	Ref #	Chemical Form	MW%	Test Organism	Phase #	# of Conc/ Doses	Conc or Doses	Study Conc or Dose Units (Units for NOAEL and LOAEL)	Method of Analyses	Route of Exposure	Exposure Duration	Duration Units	Age	Age Units	Lifestage	Sex	Effect Group	Effect Type	Effect Measure	Response Site	Study NOAEL	Study LOAEL	bw Reported	Body Weight	Body Weight Units	Body Weight (kg)	Ingestion Rate Reported?	Ingestion Rate	Ingestion Rate Unite	Ingestion Rate (kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Data Source	Dose Route	Test Substrate	Chemical form	Dose Quantification	Endpoint	Dose Range	Statistical Power	Exposure Duration	Test Conditions	Total Score
1	171	Cobalt nitrate	100	Cow (*Bos taurus*)	1	2	0/0.3	mg/kg bw/d	M	FD	45	d	7	mo	JV	F	BIO	CHM	HMGL	BL	0.3		Y	99	kg bw	99	N	na	na	3.00	0.30		10	10	10	10	10	1	4	1	10	4	70
2	116	Cobaltous chloride	100	Rat (*Rattus norvegicus*)	1	6	0/10/50/100/200/300	ppm in mg/kg	U	FD	4	w	NR	NR	NR	B	BIO	CHM	HMGL	BL	200	300	Y	150	g bw	0.15	N	na	na	0.014	19	29	10	10	5	10	5	1	10	10	10	4	75
3	19290	Cobalt nitrate	100	Rat (*R. norvegicus*)	1	2	0/20	mg/kg bw/d	U	DR	30	d	NR	NR	JV	M	BIO	ENZ	P450	LI		20	Y	175	g bw	0.175	N	na	na	0.020		20	10	5	5	10	10	1	4	10	10	4	69
4	129	Cobalt chloride	100	Rat (*R. norvegicus*)	1	2	1	mg/ml	U	DR	35	d	NR	NR	JV	M	BIO	CHM	HMCT	BL		1	Y	169.7	g bw	0.1697	N	na	na	0.020		118	10	5	5	10	6	1	4	10	10	4	65
																	…																									
6	136	Cobalt chloride hexahydrate	24.9	Rat (*R. norvegicus*)	1	2	0/75	ppm in mg/kg	U	FD	80	d	44	d	JV	M	BEH	BEH	NMVM	WO	75		Y	470	g bw	0.47	N	na	na	0.037	1.5		10	10	5	10	6	4	4	3	10	4	66
7	86	Cobalt chloride hexahydrate	100	Pig (*Sus scrofa)*	2	4	0/200/400/600	mg/kg	U	FD	28	d	NR	NR	NR	NR	BEH	FDB	FCNS	WO		200	Y	41.58	kg bw	41.58	N	1.896	na	1.47		7.1	10	10	5	10	6	4	4	10	6	4	69
8	111	Cobalt chloride	100	Rat (*R. norvegicus*)	1	2	0/20	mg/kg bw/d	M	DR	57	d	80	d	JV	M	BEH	BEH	ACTP	WO		20	Y	347	g bw	0.347	Y	34.96	g/d	0.035		20	10	5	10	10	10	4	4	10	10	4	77
10	105	Cobalt sulfate heptahydrate	21.91	Rat (*R. norvegicus*)	1	2	0/40	mg/kg bw/d	U	FD	16	w	NR	NR	NR	M	PHY	PHY	Other	HE		40	Y	0.387	kg bw	0.387	N	na	na	0.031		8.8	10	10	5	10	10	4	4	10	10	4	77
12	136	Cobalt chloride hexahydrate	24.9	Rat (*R. norvegicus*)	1	2	0/75	ppm in mg/kg	U	FD	80	d	44	d	JV	M	PTH	HIS	GHIS	NR	75		Y	470	g bw	0.47	N	na	na	0.037	1.5		10	10	5	10	6	4	4	10	10	4	73
13	116	Cobaltous chloride	100	Rat (*R. norvegicus*)	1	6	0/10/50/100/200/300	ppm in mg/kg	U	FD	4	w	NR	NR	NR	B	PTH	ORW	SMIX	TS	50	100	Y	150	g bw	0.15	N	na	na	0.014	4.8	9.6	10	10	5	10	5	4	10	10	10	4	78
14	105	Cobalt sulfate heptahydrate	21.91	Rat (*R. norvegicus*)	1	2	0/40	mg/kg bw/d	U	FD	16	w	NR	NR	NR	M	PTH	GRS	BDWT	WO		40	Y	0.387	kg bw	0.387	N	na	na	0.031		8.8	10	10	5	10	10	4	4	10	10	4	77
15	149	Cobalt chloride	100	Pig (*S. scrofa)*	1	2	0/500	ppm in mg/kg	U	FD	10	w	NR	NR	JV	M	PTH	HIS	GLSN	HE		500	Y	25.8	kg bw	25.8	N	na	na	0.99		19	10	10	5	10	6	4	4	10	10	4	73
16	113	Cobalt chloride	45.39	Mouse (*Mus musculus*)	1	2	0/180	mg/kg bw/d	U	GV	5	d	NR	NR	GE	F	PTH	GRS	BDWT	WO		180	N	36	g bw	0.036	N	na	na	0.0045		82	10	8	5	10	10	4	4	10	10	4	75
17	129	Cobalt chloride	100	Rat (*R. norvegicus*)	1	2	1	mg/ml	U	DR	35	d	NR	NR	JV	M	PTH	ORW	SMIX	HE		1	N	169.7	g bw	0.1697	N	na	na	0.020		118	10	5	5	10	5	4	4	10	10	4	67
19	126	Cobalt chloride	100	Rat (*R. norvegicus*)	1	3	0/5/20	mg/kg bw/d	U	FD	69	d	80	d	MA	M	REP	REP	TEWT	TE	5	20	N	0.21	g bw	0.00021	N	na	na	0.000065	5.0	20	10	10	5	10	10	10	8	10	6	4	83
20	124	Cobalt chloride	45.39	Rat (*R. norvegicus*)	1	4	0/12/24/48	mg/kg bw/d	U	GV	28	d	NR	NR	MA	F	REP	REP	PRWT	WO	12	24	Y	0.3	kg bw	0.3	N	na	na	0.026	5.4	11	10	8	5	10	10	10	10	10	10	4	87
21	109	Cobalt chloride hexahydrate	24.9	Rat (*R. norvegicus*)	1	4	0/25/50/100	mg/kg bw/d	U	GV	9	d	NR	NR	GE	F	REP	REP	PRWT	WO	100		Y	280	g bw	0.28	N	na	na	0.024	25		10	8	5	10	10	10	4	10	10	4	81
22	113	Cobalt chloride	45.39	Mouse (*M. musculus*)	1	2	0/180	mg/kg bw/d	U	GV	5	d	NR	NR	GE	F	REP	REP	PROG	WO	180		Y	36	g bw	0.036	N	na	na	0.0045	82		10	8	5	10	10	10	4	1	10	4	72
23	121	Cobalt chloride hexahydrate	45.39	Mouse (*M. musculus*)	1	4	0/23/42/72	mg/kg bw/d	U	DR	13	w	12	w	SM	M	REP	REP	RSUC	WO		23	Y	0.0375	kg bw	0.0375	N	6.32	na	0.0052		10	10	5	5	10	10	10	4	10	10	4	78
24	120	Cobalt chloride hexahydrate	24.9	Mouse (*M. musculus*)	1	2	0/400	mg/l	U	DR	9	w	12	w	MA	M	REP	REP	TEWT	TE		400	N	0.037	kg bw	0.037	N	na	na	0.0051		14	10	5	5	10	5	10	4	10	10	4	73
25	123	Cobalt chloride hexahydrate	100	Rat (*R. norvegicus*)	1	2	0/20	mg/kg bw/d	U	FD	70	d	100	d	SM	M	REP	REP	TEDG	TE		20	N	0.523	kg bw	0.523	N	na	na	0.040		20	10	10	5	10	10	4	4	10	10	4	77
26	119	Cobalt	100	Rat (*R. norvegicus*)	1	2	0/265	ppm in mg/kg	U	FD	98	d	100	d	MA	M	REP	REP	TEWT	TE		265	Y	200	g bw	0.2	N	na	na	0.018		24	10	10	5	4	6	10	4	10	10	4	73
27	139	Cobalt chloride hexahydrate	100	Mouse (*M. musculus*)	1	2	0/43.4	mg/kg bw/d	U	DR	13	w	12	w	MA	M	REP	REP	TEWT	TE		43.4	Y	0.045	kg bw	0.045	N	na	na	0.0061		43	10	5	5	10	10	10	4	10	10	4	78
28	187	Cobalt chloride hexahydrate	100	Mouse (*M. musculus*)	1	2	0/400	mg/l	U	DR	10	w	8 to 10	w	JV	M	REP	REP	PRFM	WO		400	N	0.0316	kg bw	0.0316	N	na	na	0.0044		56	10	5	5	10	5	10	4	10	10	4	73
30	171	Cobalt nitrate	100	Cow (*Bos taurus*)	1	2	0/0.3	mg/kg bw/d	M	FD	45	d	7	mo	JV	F	GRO	GRO	BDWT	WO	0.3		Y	99	kg bw	99	N	na	na	3.00	0.30		10	10	10	10	10	8	4	1	10	4	77
31	136	Cobalt chloride hexahydrate	24.9	Rat (*R. norvegicus*)	1	2	0/75	ppm in mg/kg	U	FD	80	d	44	d	JV	M	GRO	GRO	BDWT	WO	75		Y	470	g bw	0.47	N	na	na	0.037	1.5		10	10	5	10	6	8	4	1	10	4	68
32	86	Cobalt chloride hexahydrate	100	Pig (*S. scrofa)*	1	4	0/25/50/100	mg/kg	U	FD	16	w	NR	NR	NR	NR	GRO	GRO	BDWT	WO	100		Y	97.5	kg bw	97.5	Y	2.35	kg/d	2.35	2.4		10	10	5	10	7	8	4	10	6	4	74
33	121	Cobalt chloride hexahydrate	45.39	Mouse (*M. musculus*)	1	4	0/23/42/72	mg/kg bw/d	U	DR	5	w	12	w	SM	M	GRO	GRO	BDWT	WO	42	72	Y	0.0375	kg bw	0.0375	Y	7.8	g/d	0.0078	19	33	10	5	5	10	10	8	10	10	10	4	82
34	132	Cobalt sulfate	100	Guinea pig (*Cavia porcellus*)	1	2	0/20	mg/kg bw/d	U	OR	5	w	NR	NR	MA	M	GRO	GRO	BDWT	WO	20		Y	0.478	kg bw	0.478	N	na	na	0.037	20		10	8	5	10	10	8	4	10	3	4	72
35	111	Cobalt chloride	100	Rat (*R. norvegicus*)	1	2	0/20	mg/kg bw/d	M	DR	57	d	80	d	JV	M	GRO	GRO	BDWT	WO	20		Y	347	g bw	0.347	Y	34.96	g/d	0.035	20		10	5	10	10	10	8	4	1	10	4	72
36	116	Cobaltous chloride	100	Rat (*R. norvegicus*)	1	6	0/10/50/100/200/300	ppm in mg/kg	U	FD	4	w	NR	NR	NR	B	GRO	GRO	BDWT	WO		10	Y	150	g bw	0.15	N	na	na	0.014		0.96	10	10	5	10	6	8	4	10	10	4	77
37	109	Cobalt chloride hexahydrate	24.9	Rat (*R. norvegicus*)	1	4	0/25/50/100	mg/kg bw/d	U	GV	9	d	NR	NR	GE	F	GRO	GRO	BDWT	WO		25	Y	280	g bw	0.28	N	na	na	0.024		6.2	10	8	5	10	10	8	4	10	10	4	79
38	149	Cobalt chloride	100	Pig (*Sus scrofa)*	1	2	0/500	ppm in mg/kg	U	FD	5	w	NR	NR	JV	M	GRO	GRO	BDWT	WO		500	Y	19.8	kg bw	19.8	N	na	na	0.80		20	10	10	5	10	6	8	4	10	10	4	77
39	139	Cobaltous chloride hexahydrate	100	Mouse (*M. musculus*)	1	2	0/43.4	mg/kg bw/d	U	DR	13	w	12	w	MA	M	GRO	GRO	BDWT	WO		43.4	Y	0.045	kg bw	0.045	N	na	na	0.0061		43	10	5	5	10	10	8	4	10	10	4	76
40	129	Cobalt chloride	100	Rat (*R. norvegicus*)	1	2	1	mg/ml	U	DR	24	d	NR	NR	JV	M	GRO	GRO	BDWT	WO		1	Y	126.2	g bw	0.1262	N	na	na	0.015		122	10	5	5	10	6	8	4	10	10	4	72
42	149	Cobalt chloride	100	Pig (*S. scrofa)*	1	2	0/500	ppm in mg/kg	U	FD	10	w	NR	NR	JV	M	MOR	MOR	MORT	NR	500		Y	25.8	kg bw	25.8	N	na	na	0.99	19		10	10	5	10	6	9	4	10	10	4	78
43	113	Cobalt chloride	45.39	Mouse (*M. musculus*)	1	2	0/180	mg/kg bw/d	U	GV	5	d	NR	NR	GE	F	MOR	MOR	MORT	NR	180		Y	36	g bw	0.036	N	na	na	0.0045	82		10	8	5	10	10	9	4	10	10	4	80
44	132	Cobalt sulfate	100	Guinea pig (*Cavia porcellus*)	1	2	0/20	mg/kg bw/d	U	OR	5	w	NR	NR	MA	M	MOR	MOR	SURV	WO		20	Y	0.478	kg bw	0.478	N	na	na	0.037		20	10	8	5	10	10	9	4	10	3	4	73
Data Not Used to Derive TRV																																										
	86	Cobalt chloride hexahydrate	100	Pig (*S. scrofa)*	1	4	0/25/50/100	mg/kg	U	FD	16	w	NR	NR	NR	M	BIO	CHM	HMGL	BL	100		Y	97.5	kg bw	97.5	Y	2.35	kg/d	2.35	2.4		10	10	5	10	7	1	4	3	6	4	60
	149	Cobalt chloride	100	Pig (*S. scrofa)*	1	2	0/500	ppm in mg/kg	U	FD	10	w	NR	NR	JV	M	BIO	ENZ	GLPX	BL	500		Y	25.8	kg bw	25.8	N	na	na	0.99	19		10	10	5	10	6	1	4	3	10	4	63
	121	Cobalt chloride hexahydrate	45.39	Mouse (*M. musculus*)	1	4	0/23/42/72	mg/kg bw/d	U	DR	12	w	12	w	SM	M	BIO	CHM	HMCT	BL	72		Y	0.038	kg bw	0.038	Y	6.4	g/d	0.0064	31		10	5	5	10	7	1	4	1	10	4	60
	86	Cobalt chloride hexahydrate	100	Pig (*S. scrofa)*	3	2	0/400	mg/kg	U	FD	2	w	NR	NR	NR	NR	BIO	CHM	HMGL	BL		400	Y	23.62	kg bw	23.62	Y	0.968	kg/d	0.97		16	10	10	5	10	7	1	4	10	3	4	64

ACTP = activity level; B = both; BIO = biochemical; BL = blood; d = days; BDWT = body weight changes; BEH = behavior; bw = body weight; CHM = chemical changes; DR = Drinking water; ENZ = enyzme level changes; F = female; FCNS = food consumption; FD = food; FDB = feeding behavior; g = grams; GE = gestation; GRO = growth; GRS = gross body weight changes; GLP glutathione peroxidase; GLSN = gross lesions; GV = gavage; HE = heart; HIS = histological changes; HMCT = hematocrit; HMGL = hemoglobin; JV = juvenile; kg = kilograms; LI = liver; LOAEL = lowest observed adverse effect level; m = months; M = male; M = measured; MA = mature; mg = milligrams; MOR = effects on mortality and survival; MORT = mortality; na = not applicable; NMVM = number of movements; NOAEL = No Observed Advese Effect Level; NR = Not reported; OR = other oral; ORW = organ weight changes; P450 = changes in cytochrome P450; PHY = physiology; PRFM = sexual performance; PROG = progeny numbers/counts; PRWT = progeny weight; PTH = pathology; REP = reproduction; RSUC = resorbed embryos; SM = sexually mature; SMIX = weight relative to body weight; SURV = survival; TE = testes; TEDG = testes degeneration; TEWT = testes weight; U = unmeasured; w = weeks; WO = whole organism.

3.0 SUMMARY PLOTS OF TOXICOLOGICAL DATA

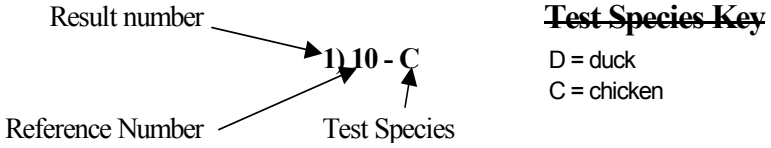
The data downloaded from the database into Excel spreadsheets is used to produce summary plots depicting the toxicological data (NOAEL and LOAEL results) for each contaminant Summary plots are constructed separately for mammalian and avian toxicological data.

3.1 Sorting by Endpoint

The data plots are organized by General Effect Group (described in Attachment 4-3) in order from left to right as:

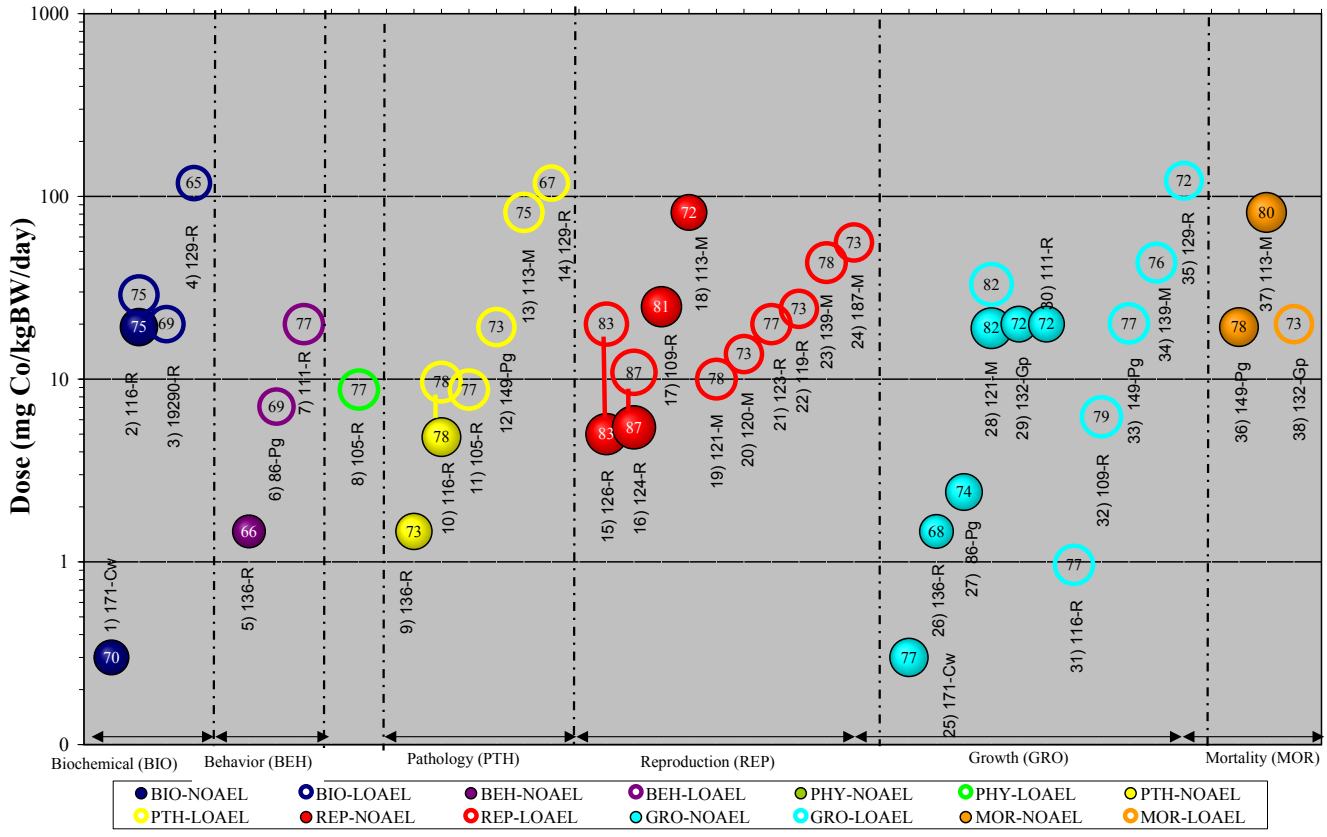
- Biochemical (BIO)
- Behavior (BEH)
- Physiology (PHY)
- Pathology (PTH)
- Reproduction (REP)
- Growth (GRO)
- Mortality (MOR)

Figure 3.1 provides an example plot showing the mammalian toxicity data for cobalt. The toxicity data associated with the plot is provided earlier as Table 2.1. The plot shows each study NOAEL and LOAEL result. NOAEL results are shown as closed circles while the LOAEL results are shown as open circles. Paired NOAEL and LOAEL values are connected by a vertical line. Within each of the circles the data evaluation score is shown and to the right of each circle the following label is shown:



The labels allow the reader to examine the plotted data and identify the relative results for different species as well as results that come from the same study. The result number allows the reader to associate that data point back to the associated toxicity data table describing more specific information for that test result.

Figure 3.1 Example Summary Plot of NOAEL and LOAEL Values



Result number → **1) 10 - C** ← Test Species

Reference Number

Test Species Key

R = rat	Pg = pig
M = mouse	Gp = guinea pig
	Cw = cow

83 ← Lowest Observed Adverse Effect Dose

← Paired values from same study when joined by line

← No Observed Adverse Effect Dose

3.2 Exclusion of Data Considered Less Applicable for Deriving a TRV

Each test result extracted during the literature review process is scored for quality and applicability for TRV derivation according to a data evaluation process as described in Attachment 4-4. In instances where more than one "experiment" (i.e., different combinations of receptor, dose, exposure route, exposure duration, and endpoint) are reported in a study, the individual "experiments" are scored separately. In cases of more than one experiment, the scoring system is applied independently to each experimental result.

The scoring system is based on evaluation of ten attributes of the toxicological study and assigns a score for each attribute, ranging from zero (no merit in setting a TRV) to 10 (extremely valuable and relevant to setting a TRV). Note that a low score does not necessarily imply the study itself is poor, only that the study design is not optimal for the narrow goal of deriving an oral TRV. The total score is calculated by adding the results of the evaluation of each attribute. Data not used for TRV derivation are defined as study endpoints receiving a Total Data Evaluation Score of 65 or less. These data points are excluded from the plots. The purpose of the exclusion is to ensure that TRV derivation uses the most suitable data. The data evaluation process and rationale is provided as Attachment 4-4.

3.3 Exclusion of Repetitive Values

Within each toxicological study there may be several effect measures reported that have the same NOAEL and/or LOAEL values. Inclusion of the NOAEL and LOAEL results for all endpoint measures may result in repetitive values. To avoid the inclusion of repetitive and duplicative data, the results for only one Effect Measure per Effect Group are recorded in the plots. As described previously there are seven possible General Effect Groups so a unique study may yield up to seven results each that are extracted and plotted.

For example a study provides the following results:

General Effect Group	Effect Type	Effect Measure	NOAEL	LOAEL
BIO	CHM	TRIG	5	10
BIO	CHM	GLUC		5
BIO	ENZ	ACHE	5	10

There are results for three effect measures reported within the general effect group biochemical (BIO). In this instance, the most conservative result is recorded for BIO/CHM/GLUC with a LOAEL of 5 and the other effects are noted in the comment fields of the TRV database as instruction in Attachment 4-3.

4.0 PROCESS FOR DERIVATION OF WILDLIFE TRVs

4.1 TRV Definition

For the purposes of establishing the Eco-SSLs, the wildlife TRVs are defined by the workgroup as:

> *Doses above which ecologically relevant effects might occur to wildlife species following chronic dietary exposure and below which it is reasonably expected that such effects will not occur.*

4.2 Goals and Assumptions

The following underlying goals and assumptions guided the development of the TRV derivation process.

Use Chronic Exposure Data

The Wildlife TRV should be based on chronic effects data and not acute or subacute toxicity information (exposures of 3 days or less in duration). The purpose for exclusion of acute toxicity data was to focus efforts on establishing a dose protective of most species from adverse effects associated with long term exposures and sublethal reproductive and growth effects. A chronic exposure duration is that of sufficient length to reveal most adverse effects that will occur, or would be expected to occur, over the lifetime of an exposed organism (NAS, 1980; USEPA, 1985).

Consider All Toxicological Information.

The TRV should be based on the examination of all toxicological data extracted. These data are plotted and examined in a weight-of-evidence fashion as described in Section 4.4. The TRVs should not be based on the selection of a single "critical" study.

Consider Only Results for Dietary or Other Oral Exposures.

The wildlife TRVs should consider only oral dose response data. These data are considered the most relevant to establishing soil screening levels that are protective of potential oral exposures (ingestion of soil or food). Toxicological data for non-oral exposure routes are excluded from the literature search and literature evaluation processes as described in Attachments 4-2 and 4-3.

4.3 Methods Considered for TRV Derivation

The task group responsible for derivation of wildlife TRVs considered many different approaches for establishing these values. Some, but not all, of the methods considered are discussed here to provide context for the method developed for TRV derivation.

Critical Study Approach

One method considered was the selection of a critical study result for each contaminant for mammals and birds. The study result would then be used as the TRV or a series of extrapolation and/or uncertainty factors would be applied to the critical study result to achieve the TRV. Factors are typically applied for "normalization" of the data such as approximating the chronic result from either acute or subchronic exposure data or approximating the NOAEL from the LOAEL. Other factors can be applied to the critical study result to account for "uncertainty" and ensure the protectiveness of the value and this would include factors for interspecies sensitivity. The critical study approach is currently used by EPA for human health risk assessments with toxicity values made available in the Integrated Risk Information System (IRIS). The critical study approach was also used in the derivation of wildlife criteria for the Great Lakes Water Quality Initiative (GLI) (USEPA, 1995); by Sample et al. (1996) for the derivation of wildlife screening benchmarks for the Oak Ridge National Laboratory Reservation; and by the Canadian Council of Ministers of the Environment (CCME) for soil quality guidelines for livestock and wildlife (CCME, 1997).

The Eco-SSL task group chose to use a broader "weight-of-evidence approach"(further described in Sections 4.4 and 4.5) that considered all of the extracted toxicological data in place of the selection of one critical study. The use of the critical study approach would require considerable professional judgement thereby decreasing the transparency and reproducibility of the wildlife TRV derivation process. To avoid foreseen conflicts over selection of "one" result; to prevent the need for "committee" selection and to attain transparency and reproducibility this method was not selected.

Benchmark Dose Approach

In recent years, the benchmark dose approach has been examined for use in human health risk assessments in place of NOAEL and LOAEL approaches (Rees and Hattis, 1994; USEPA, 1995). The benchmark dose is defined by EPA as the statistical lower confidence limit for a dose that produces a predetermined change in response rate of an adverse effect (called benchmark response) compared to background (USEPA, 1995).

Use of a benchmark dose method requires not only the selection of a critical study but also the critical or benchmark response within that study that would be modeled. It is also necessary to select the appropriate model or model(s) for the experimental data to derive the benchmark dose. The benchmark dose approach has not been adopted for use by the ecological risk community and a margin of safety or the acceptable "predetermined change in response rate"has not been identified by the regulatory community. With these limitations as well as those discussed for the critical study approach, the benchmark dose approach was not selected for derivation of the wildlife TRVs for Eco-SSLs.

Distribution Approaches

Using distributions to represent the species sensitivities to contaminants is commonly used. The approach assumes that "...sensitivity of species is a stochastic variable that can be characterized by fitting a probability density function to test endpoints (e.g., LD50's LC50's for several species (Suter, 1993). This approach is used to establish soil standards in the Netherlands (Van Straalen and Denneman, 1989). Uncertainty is incorporated in the determination of confidence limits for thresholds protective of a fixed percentage of species (Van Straalen and Denneman, 1989; Aldenberg and Slob, 1993). As the sample size of the number of species tested increases, the protection threshold also increases.

Forbes and Forbes (1993) provides a review of the limitations of the distribution-based extrapolation models. The authors question the underlying assumptions of these models including: 1)"the distribution of species sensitivities in natural ecosystems closely approximates the threshold distribution"; 2) "the sensitivity of species used in laboratory tests provide an unbiased measure of the variance and mean of the sensitivity distribution of species in natural communities"; 3) "by protecting species composition, community function is also protected"; and 4) "interactions among species in communities and ecosystems can be ignored".

Within the ECOFRAM guidelines a distribution based approach is used to predict the 5th percentile of the species sensitivity distribution based on the oral LD50 or LC50. With birds the minimum number of species required to use the distributional approach for species sensitivity is established by Luttik and Aldenberg (1995) at four. When N is equal to 4 or more species the parameters of the distribution are determined by the use of extrapolation factors from Aldenberg and Slob (1993). In cases, where n is less than four, then the 5th percentile is predicted based on pre-determined extrapolation constants that compensate for small sample size (ECOFRAM, 1999).

The distributional methods recommended for use in ECOFRAM are not however recommended for use with the avian reproduction study (a 14 day exposure) as the toxic mechanisms are different from the ones involved with acute toxicity. In a review of reproduction studies done with the Mallard and Bobwhite Quail by Mineau, Boersma and Collins (1994) the developmental effects differed significantly between the two species and there was greater similarity between the rat and bird results than between that of the two bird species. This suggests a limited ability to extend the results of the avian reproductive test or any other chronic test that identifies no-effect and low-effect values to other bird species.

The use of distributional approaches is also limited by the non-comparability of the results reported for chronic exposures in the literature. The literature available reporting chronic toxicity of contaminants to laboratory test animals and wildlife reflects a wide range of endpoints, exposure durations, test species, exposure routes, test conditions and all (most) using different non standardized testing protocols. The chronic testing results are consequently non-comparable and inappropriate for plotting as a distribution. The distributional approach advocated for use within ECOFRAM and others is dependant upon the availability of

comparable results (LD_{50} values) from a standard toxicity testing protocol with the same toxicity endpoint, exposure duration, test species, exposure route and test conditions.

As a result of the earlier stated deficiencies and concerns with distributional approaches, and primarily the lack of an adequate toxicological database, the distributional approach was not selected for use.

Weight-of-Evidence Approach

In a weight-of-evidence approach the TRV is selected based on the preponderance of the data. With this approach, all toxicological data (NOAELs and LOAELs) extracted (Attachment 4-3) from the studies identified in the literature review (Attachment 4-1) and determined to be appropriate in establishing a TRV (as described in Attachment 4-4) would be plotted and the relative magnitude of the results examined to identify a threshold that would be protective. Examination of the dose-response data replaces the use of extrapolation factors as recommended by Chapman et al. (1998). The use of this method avoids the problems previously discussed with regard to the critical study approach.

4.4 Derivation Method Selected

The specific method selected for use in the derivation of TRVs is a "weight-of-evidence" approach that includes the use of some factors (adjustments) to account for uncertainties. All NOAEL and LOAEL values extracted (Attachment 4-3) from studies identified in the literature review (Attachment 4-2) and scored according to the data evaluation scoring procedure (Attachment 4-4) are plotted as described in Section 3.0. The resulting relative magnitude of the NOAEL and LOAEL values by effect type (biochemical, behavioral, physiological, pathology, growth, reproduction and mortality) are examined in a relative manner to identify or calculate a threshold value as the TRV according to the specific procedure described in Section 4.5. In most cases the TRV is equal to the geometric mean of NOAELs for GRO and REP effects. The use of NOAEL and LOAEL values as the basis of the wildlife TRV derivation process is deemed a reasonable and effective approach when these values are presented across multiple studies, species, and endpoints as depicted in the toxicological plots (Figure 3.1).

The LOAEL is defined as the lowest concentration (or dose) at which statistically significant adverse effects are observed in the test organism compared to controls. The No-observed adverse effect level (NOAEL) is defined as the highest experimental dose that is not associated with significant adverse effects in the test organism compared to controls.

The process developed for derivation of the wildlife TRVs is designed specifically to address some of the stated limitations and concerns in using NOAEL and LOAEL results for establishing threshold dose-response values. These limitations and concerns are previously discussed in several publications (Chapman et al., 1998; USEPA, 1995; Hoekstra and Van Ewijk, 1993; Chapman et al., 1996; Dhaliwal et al., 1997; and Chapman and Chapman, 1997). Some of the stated concerns and how they are addressed by the process are discussed as the following bullets:

2) The experimental dose referred to as the NOAEL is often based on judgement. The process developed for extraction of toxicity data (the NOAEL) (Attachment 4-3) and the data evaluation score (Attachment 4-4) include clear guidance on how to choose or select the NOAEL value from the toxicological study. The NOAEL and LOAEL results are examined to ensure they are accurately represented by the author. Primarily, the adequacy of the statistics used and the absence or presence of a dose dependant response are evaluated and considered in the identification of the NOAEL.

   The evaluation of the experimental design includes the dose ranges and statistical power. NOAELs with lower statistical power and wider or fewer dose ranges are given lower data evaluation scores. NOAELs with a data evaluation score of 65 (out of 100) or less are not used in the derivation of the TRV.

3) Experiments involving fewer animals tend to produce higher NOAELs and thus higher TRVs. The statistical power of the NOAEL is determined in part by the number of experimental animals. In the TRV derivation process, NOAELs with lower statistical power are given lower data evaluation scores. Also, the examination and use of NOAELs from multiple studies and multiple endpoints (in place of one study result) reduces the influence of any one study design in the calculation of the TRV.

4) The slope of the dose response curve plays little role in determining the NOAEL. The goal of the wildlife TRV derivation process is to identify a "no effect" concentration for purposes of deriving a soil screening value. Ideally, this "no effect" level should be close to the threshold for effects but this may not be true and the NOAEL consequently may be too low. As the wildlife TRV is based on multiple NOAELs across many studies, endpoints, and species this type of error for any individual study result is considered to be of little consequence.

5) The NOAEL cannot be used to characterize the magnitude of effects. The NOAEL value cannot be used to characterize the magnitude of any adverse effects. This is why LOAEL values are also included in the wildlife TRV process as a point of comparison with NOAELs and are also used to identify the TRV.

6) The NOAEL is affected by study design including the number and spacing of doses, endpoints measured and the number of replicates in each dose. The dose-response curve is also influenced by the study design. The examination and use of NOAELs from multiple studies and multiple endpoints (in place of one study result) reduces the influence of any one study design in the calculation of the TRV.

The use of NOAEL and LOAEL values as the basis of the wildlife TRV derivation process is deemed a reasonable and effective approach when these values are presented across multiple studies, species, and endpoints as depicted in the toxicological plots (Figure 3.1). These results are examined in a relative manner to identify or calculate a threshold value as the TRV according to the specific procedure described in Section 4.5. The minimum data sets required for the

procedure as well as the consideration of interspecies sensitivity are described in the following subsections.

4.4.1 Minimum Data Set Required to Derive a Wildlife TRV

The task group identified a minimum data set required for derivation of either the mammalian or avian TRV. This minimum data set is based on discussions within the workgroup and best professional judgment. Once the toxicological study data is reviewed and input into the wildlife TRV database (Attachment 4-3) the data will be examined to evaluate intraspecific sensitivity. This analysis may result in changes to the minimum data set. The required data set consists of three NOAEL or LOAEL results for at least two test species for either growth (GRO); reproduction (REP) or survival (MOR) effects.

The minimum data set is generally consistent with minimum data sets established for other soil and risk guidelines. The Canadian Soil Quality Guidelines (CCME, 1997) requires a minimum of three studies for calculation of soil quality guidelines for soil and food ingestion for livestock and wildlife. There is a further requirement that at least two of these studies be oral mammalian studies and one must be an oral avian study. A maximum of one laboratory rodent study may be used to fulfill the data requirements for mammalian species if needed. Toxicity testing of pesticides prior to registration generally requires only one or two standard test species (ECOFRAM, 1999). However, the minimum number of avian species required to use the distributional approach for species sensitivity is established by Luttik and Aldenberg (1995) at four.

4.4.2 Interspecies Sensitivity

For technical and fiscal reasons only a few species of wildlife can be tested for toxicity of contaminants. Only rarely are test species the same as those likely to be exposed under field conditions. This fact implies that test results from standard test species need to be extrapolated to most field species.

Several investigators have examined the inter-species sensitivity of avian species to pesticides. The interspecies extrapolation methods recommended by ECOFRAM as part of the FIFRA risk assessment methods are based on analyses of 20 years of acute oral toxicity studies (LD50 study) on pesticides. The oral LD50 data reflects a large number of tests completed for many species for numerous compounds using only one well established test protocol. Analysis of this data by Baril et al. (1994) resulted in the following observations:

(1) Ranking of species sensitivities tends to persist across chemicals

(2) Red-winged blackbirds are the most sensitive followed as a group by the Common Grackle, the House Sparrow, the Mallard and the Rock Dove. A second group including the Pheasant, Japanese Quail and the Starling are the least sensitive.

Other authors (Joermann, 1991; Schafer and Brunton, 1979; and Tucker and Haegele, 1971) have also evaluated phylogenetic patterns in sensitivity of avian species to pesticides. These studies have demonstrated some patterns of sensitivity between some families of birds across pesticides. However, each species shows a wide range of sensitivity among the same pesticides. ECOFRAM concludes that there are probably enough exceptions to prevent the development of a predictive approach based on phylogenetic relationships. They did conclude that two groupings of species (based on taxonomic relationships) could be separated according to sensitivity (acute) to cholinesterase-inhibiting chemicals (ECOFRAM, 1999).

As more data becomes available in the Wildlife TRV database, interspecies sensitivity will be further examined by comparison of bounded LOAEL values between species by contaminant. This approach is similar to that used to examine the use of uncertainty factors for wildlife criteria in the GLWQI. If the current minimum data set is deemed underprotective then the minimum data set and the use of additional uncertainty factors will be re-evaluated.

4.5 Specific Procedure for Derivation

The general steps and conditional statements of the derivation process are outlined in Figure 4.1. These steps are an a priori framework for selection or calculation of the TRV value based on the results of the NOAEL and LOAEL data plots. The flow chart is used with the toxicological data plots to derive the TRV according to the following described steps.

Step 1: Are there at least 3 results and 2 species tested for reproduction (REP), growth (GRO) or mortality (MOR) general effect groups?

The minimum data set required to derive either a mammalian or avian TRV consists of three results (NOAEL or LOAEL values) for REP, GRO or MOR for at least two mammalian or avian species. If these minimum results are not available then a TRV is not derived.

Step 2: Are there 3 or More NOAELs in REP and GRO Effect Groups?

Calculation of the geometric mean NOAEL for REP and GRO requires at least three NOAEL results from either of the GRO, REP or MOR effect groups. If three or more NOAEL results are available then the user proceeds to Step 4. If there are less than three NOAEL results, then the user proceeds to Step 3.

Step 3: Is there at least one NOAEL for REP and GRO?

If there is at least one NOAEL result available for the REP and GRO effect groups, then the TRV is equal to the lowest reported NOAEL for either effect group (GRO or REP). In cases where this NOAEL is higher than the lowest LOAEL for the MOR effect group then the TRV is equal to the highest NOAEL below the lowest LOAEL for the MOR effect group or the lowest LOAEL which ever is lower.

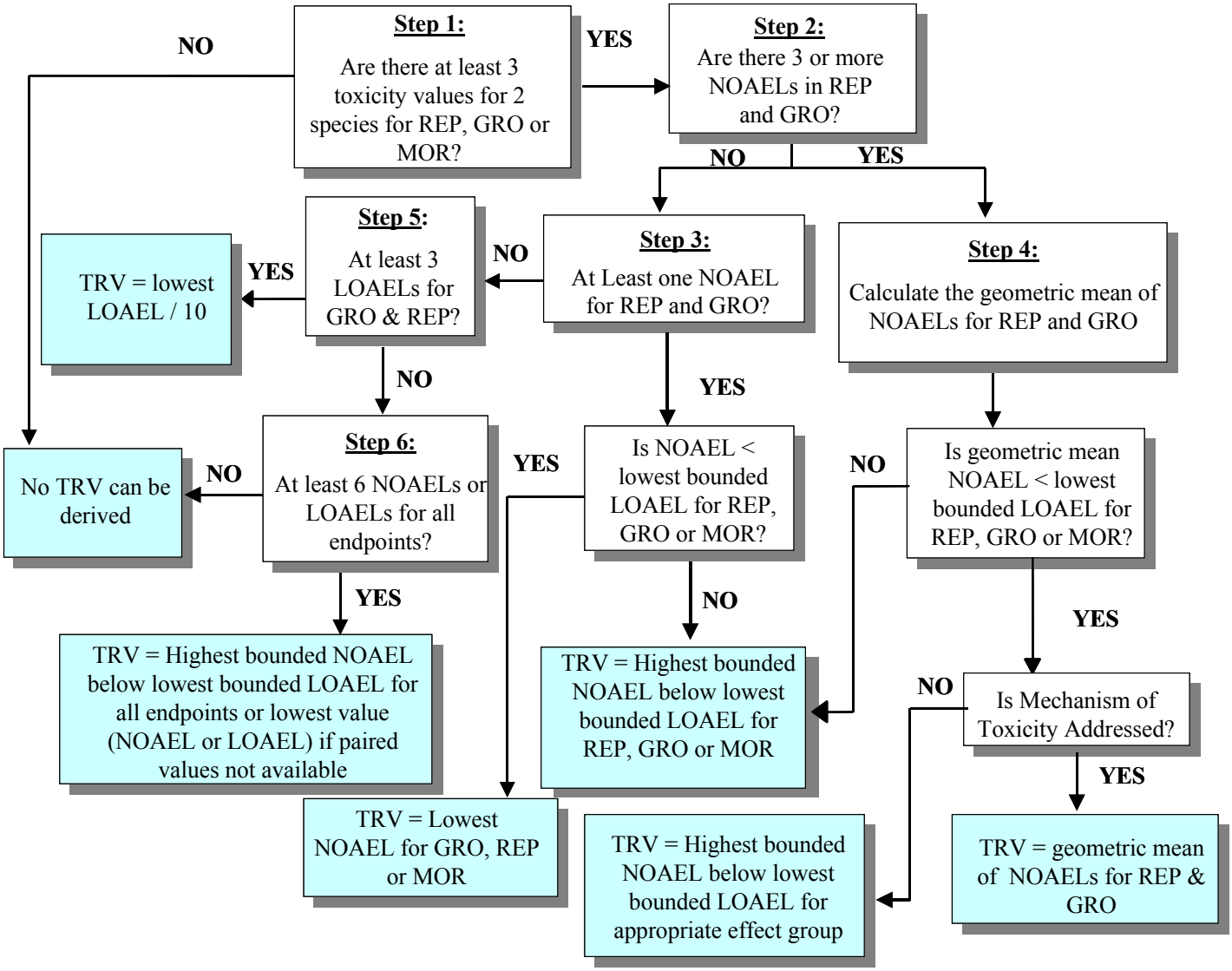


Figure 4.1 TRV Derivation Procedure

Step 4: Calculate a geometric mean of NOAELs for GRO and REP Effect groups.

The TRV is equal to the geometric mean of the NOAEL values in the REP and GRO Effect Groups with the following exceptions.

Is the Geometric Mean NOAEL greater than the highest bounded NOAEL below the Lowest bounded LOAEL for REP, GRO or MOR?

In some cases the geometric mean NOAEL (REP and GRO) may be higher than the highest bound NOAEL (paired NOAEL and LOAEL values) below the lowest bound LOAEL value for results within the REP, GRO or MOR effect groups. In other words, the geometric mean NOAEL value may not be sufficiently protect all tested species and represent the threshold of REP, GRO, and MOR effects. In these instances, the TRV is equal to the highest bound NOAEL below the lowest bound LOAEL value for results within the GRO, REP and MOR effect groups.

Is the mechanism or mode-of action of toxicity addressed by the Effect Measures in the GRO, REP and MOR Effect Groups?

If the mechanism, or mode-of-action of toxicity, is not addressed by the Effect Measures in the GRO, REP and MOR Effect Groups then the TRV is equal to the highest bound NOAEL below the lowest bound LOAEL for the appropriate effect group. This possible pathway for TRV derivation is included to allow the toxicologist to set a TRV based on the data most appropriate for the particular contaminant.

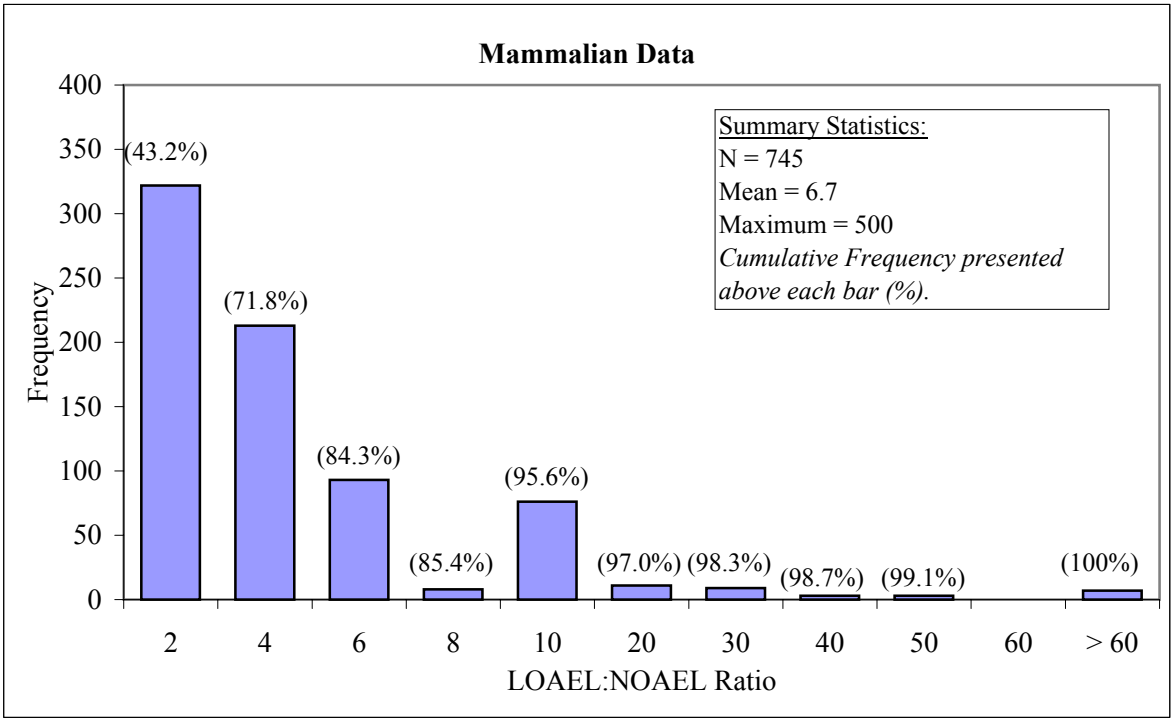
Step 5: Are there at least 3 LOAELs for GRO & REP?

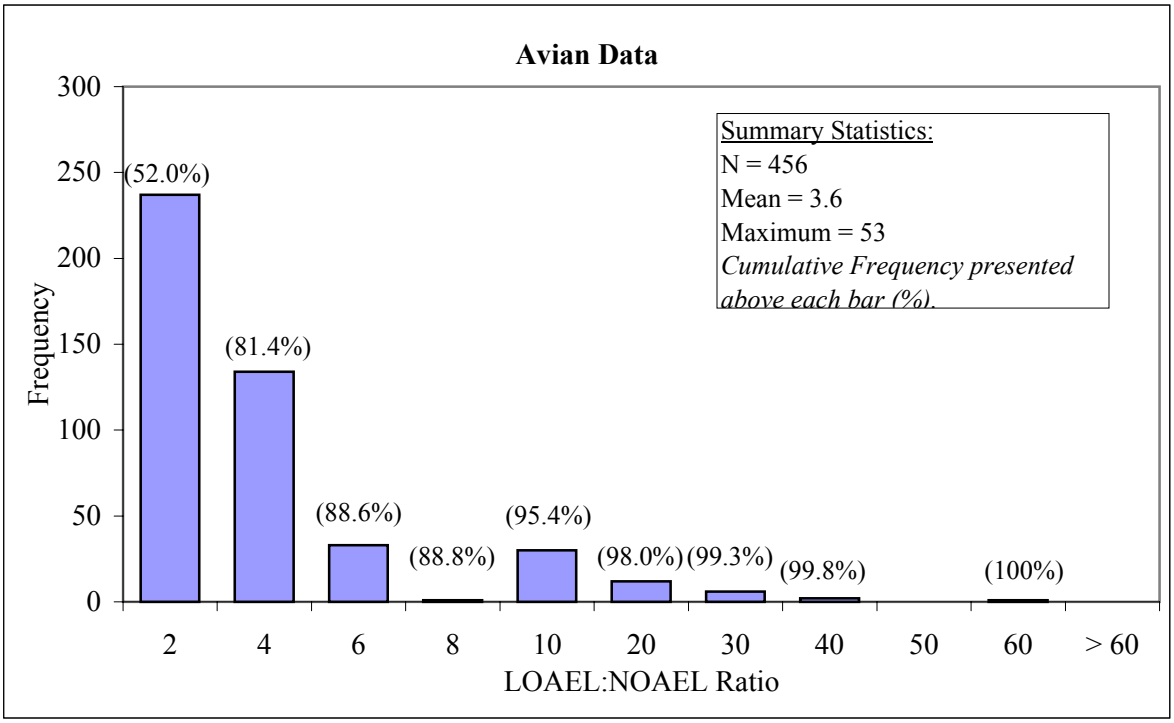
If there are at least 3 LOAELs for GRO and REP then the TRV is equal to the lowest LOAEL divided by an uncertainty factor. If there are less than 3 LOAELs then the user goes to Step 6.

The uncertainty factor is intended to extrapolate from the LOAEL (lowest observed effect) to a NOAEL (no observed effect) value. In order to derive an UF to approximate the NOAEL from the LOAEL, the LOAEL to NOAEL ratios (bounded) in the Wildlife TRV database were examined (Figure 4.2). To date there are 456 paired LOAEL/NOAEL values in the database for avian species and 745 for mammalian species. With this data the ratios of bounded LOAELs NOAELs are described in Figure 4.2.

Approximately 84.3% of the LOAEL values for mammals and 88.6% for birds are within a factor of 5 of the respective paired NOAEL value (Figure 4.2). Approximately 96% and 95% of the values are within a factor of 10 for mammals and birds, respectively. As the purpose of the TRV is for calculation of (conservative) soil screening values, a value of 10 was chosen as the UF as 97% of the cases within the wildlife TRV database, the NOAEL is within a factor of 10 of the LOAEL. This quantitative result is not surprising. Dosing studies are commonly designed with order of magnitude increased in dose (e.g., 1, 10, 100, 1000).

Figure 4.2
LOAEL to NOAEL Ratios in Wildlife TRV Database





Therefore, threshold approaches will consequently most likely end up with a factor of 10 between NOAEL and LOAEL values.

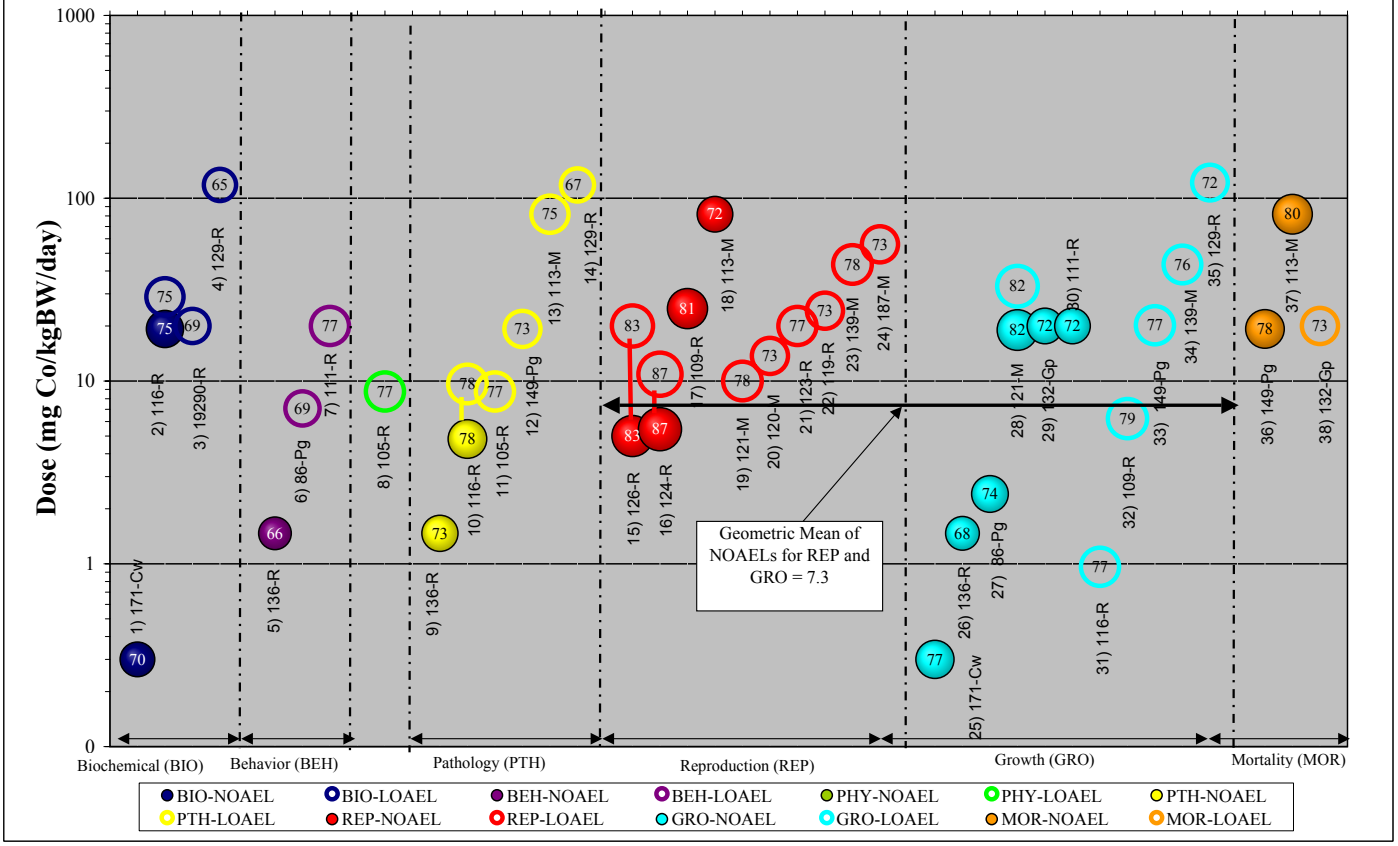
Chapman et al (1998) and e,p&t (1996) criticize the use of the LOAEL in approximating a NOAEL dose. They argue that LOAEL determination is a function of the spacing of dietary concentrations and statistical power of the test and that LOAELs are often incorrectly low due to statistical artifacts and that these uncertainties are compounded when the LOAEL is divided by an uncertainty factor. While it is true that NOAEL and LOAEL determination is function of study design, it is hoped that the NOAEL and LOAEL brackets the threshold. As many LOAELs may be incorrectly low it is assumed that the use of an UF equal to10 will successfully bracket the lower range of the possible threshold (NOAEL). This UF value will be updated as more toxicological data becomes available within the TRV wildlife database.

For the contaminants for which TRVs have been derived to date, there has not been an instance where this step was used to derive a TRV. All contaminants examined to date have either had sufficient data to derive a TRV based on NOAEL values or data is not available at all (e.g., antimony, barium and beryllium for birds).

Step 6: Are there at least 6 LOAEL values available for other endpoints?

In cases where there are less than three LOAEL values available for all GRO or REP Effect groups, the TRV can be derived based on the available LOAEL values for other Effect Groups (BEH, PTH, BIO, PHY, MOR). As this type of dose-response data is considered to be less useful for establishing a TRV twice the number of data points are required as a minimum to derive a TRV (compared to data for GRO, REP and MOR). The highest NOAEL below the lowest LOAEL for all effect Groups are identified and the lowest of these is identified as the TRV. If bounded values are not available, then the TRV equals the lowest NOAEL or LOAEL for all endpoints. If less than six total NOAEL or LOAEL values are available then a TRV cannot be derived.

Figure 4.3 Example of TRV Derivation



Result number → 1) 10 - C ← Test Species

Reference Number

Test Species Key

R = rat
M = mouse
Pg = pig
Gp = guinea pig
Cw = cow

83 — Lowest-Observed Adverse Effect Dose
Paired values from same study when joined by line
No-Observed Adverse Effect Dose

Wildlife TRV Derivation Process

1) There are at least three results available for two test species within the growth, reproduction and mortality (survival) effect groups. There is enough data to derive TRV.

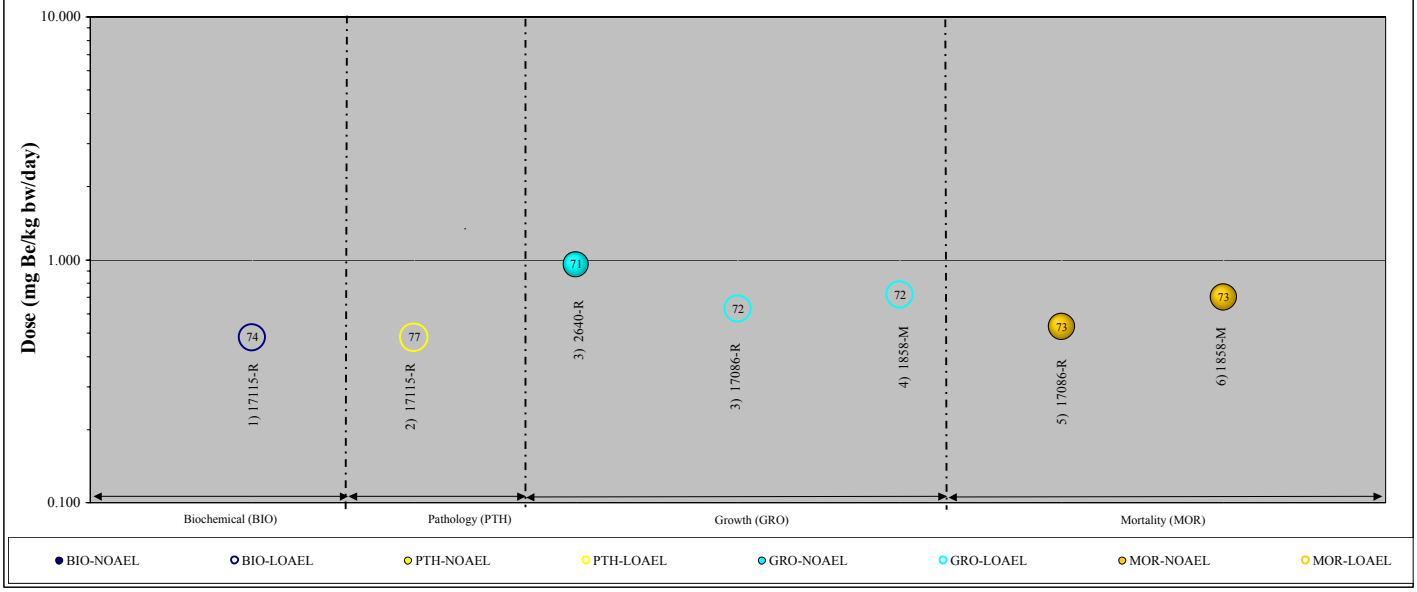
2) There are are at least three NOAEL results available for calculation of a geometric mean.

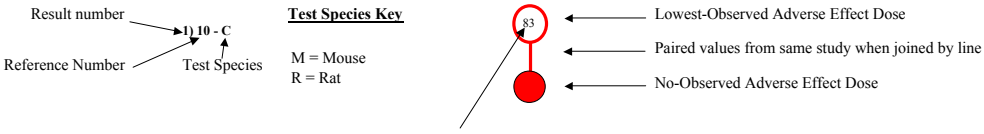
3) The geometric mean of the NOAEL values for growth and reproduction equals 7.3 mg Co/kg BW/day.

4) The geometric mean NOAEL value is less than the lowest bounded LOAEL for reproduction, growth or survival.

5) The mammalian wildlife TRV for cobalt is equal to 7.3 mg Co/kg BW/day.

Figure 4.4 Example of TRV Derivation





Wildlife TRV Derivation Process

1) There are at least three results available for two test species within the growth, reproduction and mortality effect groups
There is enough data to derive a TRV

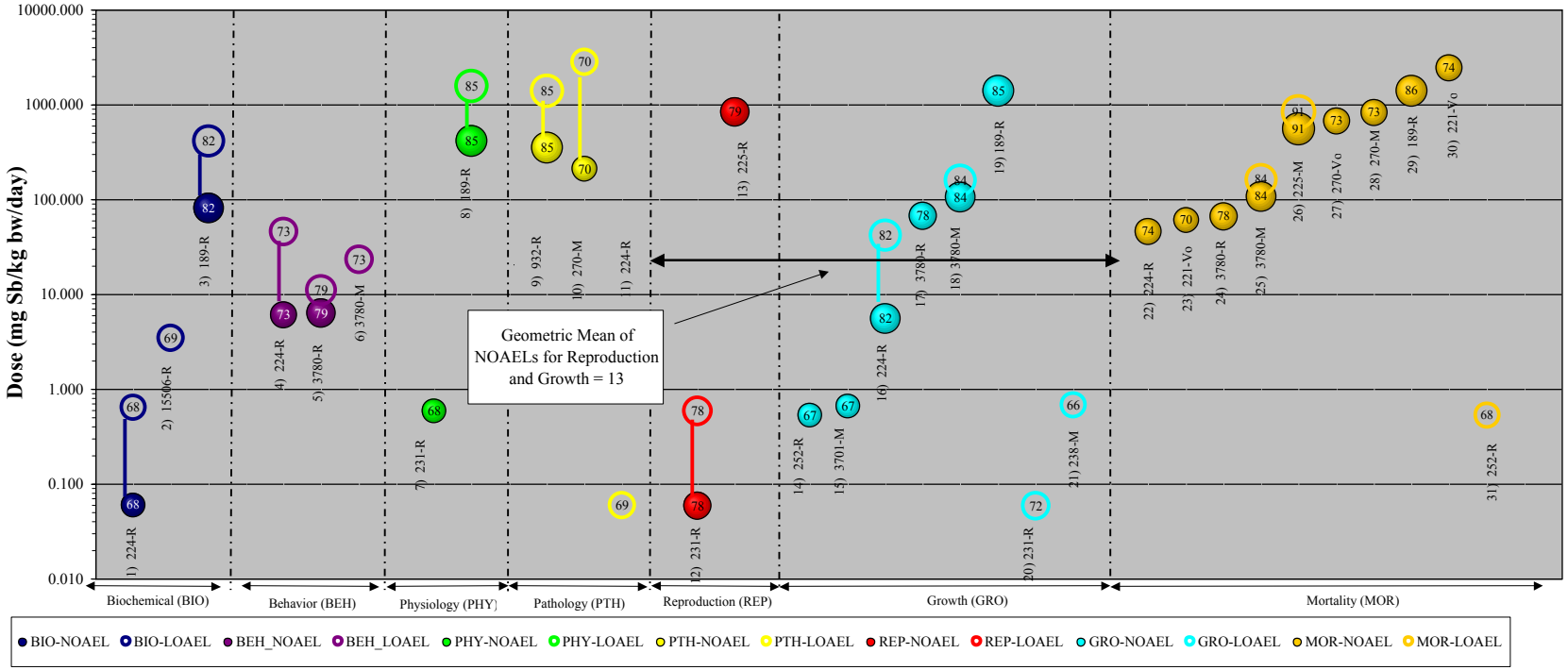
2) There are not three NOAEL results available for calculation of a geometric mean

4) There is one NOAEL value for reproduction or growth effects

5) There are no bounded LOAELs for comparison. The TRV is equal to the lowest NOAEL for effects on growth, reproduction or surviv

6) The mammalian wildlife TRV for beryllium is equal to 0.48 mg Be/kg bw/day which is the lowest NOAEL for effects on growth, reproduction and survi

Figure 4.5 Example of TRV Derivation



Result number → 1) 10 - C ← Test Species

Reference Number

Test Species Key

Vo = Short-tailed field vole
M = Mouse
R = Rat

83 ← Data Evaluation Score

Lowest-Observed Adverse Effect Dose

Paired values from same study when joined by line

No-Observed Adverse Effect Dose

Wildlife TRV Derivation Process

1) There are at least three results available for two test species within the growth, reproduction and mortality effect groups. There is enough data to derive a TRV.

2) There are are at least three NOAEL results available for calculation of a geometric mean.

3) The geometric mean of the NOAEL values for growth and reproductive effects equals 13 mg Sb/kg BW/day.

4) The geometric mean NOAEL value is higher than the lowest bounded LOAEL for reproduction, growth, or mortality effects

5) The mammalian wildlife TRV for antimony is equal to 0.059 mg Sb/kg BW/day which is the highest bounded NOAEL below the lowest bounded LOAEL for reproduction, growth or mortality effects.

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