A Repair for Non-Cancer Assessment: Introducing the Truly Adverse Dose (the TAD)

Lawrence Tannenbaum, senior health risk assessor, certified senior ecologist

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Basic background

- We live in a chemically contaminated world, and we have an environmental health risk assessment process because of it.
- There is a real need to know how toxic chemicals may be to chronically exposed humans. That said, we recall that it's simply not ethical to deliberately expose humans to chemicals.
- For human health risk assessment (HHRA) purposes, we've no choice but to dose animals, and to learn from their responses.

Yes, of course, there are "NAMs" (that's "New Approach Methodologies") today, such as 'organ-on-a-chip', but this might not be the panacea that some expect it to be.

Basic background, cont'd.

- An unavoidable consequence of employing animals as test subjects is the need to extrapolate animal responses to human ones. It is here that four key unknowns arise for which we should endeavor to solve.

- Is the observed effect in the test animal, adverse for the test animal?
- Does the chemical when administered to a human, produce the same effect observed in the test animal?
- Assuming the same effect *is* produced in the human, does the equivalent chemical dose produce the same magnitude of response in the human as that observed in the test animal?
- Should it be that humans respond after the fashion of laboratory test animals, is the human response adverse?

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Basic background, cont'd.

Is the observed effect in the test animal, adverse for the test animal?

- Talking sublethal systemic effects (other than *lesser reproductive output* and *neurological/behavioral impairment*), we *could* know the answer to this question, but we don't make an effort to pursue it.
- Instead, we simply assume that the sublethal effects we observe are toxic/adverse. But are they?
- Since they're going to be used as the toxicological bases of noncancer/systemic effect HHRA assessments, we should size up animal study-based oral Reference Doses (RfDs) (as we have them in IRIS) asking . . .

Can we comfortably extrapolate from the underlying studies to human health risk assessments; HHRAs?

Mini review: Where RfDs come from[1]

- Every critical study supporting an RfD has used several doses.
- Ideally, each study produces an effect level, termed an "adverse effect level". It's the dose below the (adverse) effect level that is taken to be the NOAEL, which, by definition, is safe.
- Conventional HHRA wants to know if a given human receptor is taking a (site) noncarcinogen into his/her body at, above, or below the safe level. Everything good so far?

[1] Sincere apologies for this mini review, but we must be sure everyone is on the 'same page'.

Mini review, cont'd.

- A chronic study (of course) orally dosed animals at: 0, 25, 100, | 400, and 800 mg/kg.
- An effect occurred a 400 mg/kg.
- The NOAEL then, is necessarily 100 mg/kg. (Bear in mind that 200 or 300 mg/kg could also be safe.)
- The 100 mg/kg NOAEL is divided by the combined relevant Uncertainty Factors (UF) and Modifying Factor (MF) to produce the oral RfD. If the product of the UF and MF was say, 3,000, the oral RfD is . . . **3.33E-02 mg/kg**. **Got it?**
- Time then, to *dice up and slice up* the U.S. EPA Regional Screening Level (RSL) Table.

An analysis of RSL Table oral RfDs (starting with an initial universe of 649 chemicals[1])

Basis for eliminating a noncarcinogen from analysis	Number of chemicals removed
lower position in the peer-review hierarchy[2]	247
recently archived pesticides	51
Other archived chemicals	3
BMD as basis of RfD	33
human or avian study as basis	9
critical effect "not available"	17
[1] From the 2017 RSL Table [2] Other than IRIS	∑ **360** (**289** chemicals with oral RfDs retained)

Toxicological bases of (the retained) oral RfDs

Toxicological basis	Frequency of occurrence (%)
NOEL	43.1
NOAEL	40.1
	∑83.2
LEL	11.6
LOAEL	3.9
	∑15.5

What's the "A" stand for?

As it should be, but . . . what's the difference between a NOEL and a NOAEL?

<u>Not</u> as it should be. And what's the difference between an LEL and a LOAEL?

Critical study outcomes . . .

- Ideally, a tox study should produce both a NOAEL and a LOAEL. For **26%** of the critical studies supporting oral RfDs though, only one or the other of these was furnished. ☹

- An absent NOAEL (occurring **17%** of the time) means that every test dose produced an adverse response. One's only recourse is to take the lowest dose and apply (somewhat augmented) UFs to get the RfD. (Think 0, 100, 200, 400, 800.)

- An absent LOAEL (occurring **9%** of the time) means that every test dose was a safe one. Conceivably multiples of the highest test dose are also safe! (Think 0, 100, 200, 400, 800.)

A Fair Question to ask: How do studies that fail to supply the requisite toxicity information for RfD-setting, come to be selected as "critical studies"?

Uncertainty Factor Magnitude Analysis
(a look at UFs when critical tox information is absent)

Condition	Arithmetic mean of UFs	Geometric mean of UFs
Case 1: **essential toxicological information available**: (a no-effect level and an effect level were furnished)	626.6	273.7
Case 2: **essential toxicological information lacking**: (a no-effect level or an effect level were furnished, but not both)	1732.1	770.3
Ratio of UF means: $\frac{\text{critical study lacking some essential information}}{\text{critical study with essential information}}$	2.76	2.81

‘member this slide?

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A ‘by-decade review’ of critical study dose-gapping

Decade in which critical studies were conducted	Percentage of critical studies (of the selected universe) conducted during a given decade	Ratio of LEL/LOAEL to NOEL/NOAEL
1950 - 1959	3	5.25
1960 - 1969	11.8	7.31
1970 - 1979	17.7	4.82
1980 - 1989	60.6	8.24
1990 - 1999	5.4	6.00
2000 - 2009	1	5.56

A ‘by-decade review’ of critical study dose-gapping

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1950 - 1959	3	**Uh-oh! Over 90% of IRIS critical studies pre-date the advent of HHRA!**	5.25
1960 - 1969	11.8		7.31
1970 - 1979	17.7		4.82
1980 - 1989	60.6		8.24
1990 - 1999	5.4		6.00
2000 - 2009	1		5.56

The essential point:

"... because ... studies were not designed to identify the point at which safe doses give way to harmful effect levels, the spacing of test doses within a given study tends to be greater than what we know today to be highly desirable. The greater the distance between a study's no effect and effect levels, the greater the chance a selected NOAEL will be unnecessarily low, which, in turn, can lead to an exaggerated HQ."

Source: Tannenbaum and Comaty. 2019. HERA Vol. 3:624-636

Understanding noncancer hazard assessment . . .

- For noncancer (hazard) assessment to work, it is **imperative** that a chemical have the capability to produce **an adverse effect** -- not just that exposure to the chemical causes an “effect” (a change; a shift; a difference, etc., etc.).
- Once we know that there can be an adverse effect, then we can go about finding a safe (exposure) dose for the chemical. Noncancer (hazard) assessment is about determining how much more than a chemical’s safe dose a receptor is ingesting, inhaling, or dermally contacting.

Key: I = IRIS; P = PPRTV; O = OPP; A = ATSDR; C = Cal EPA; X = APPENDIX PPRTV SCREEN (see FQ #31); H = HEAST; F = See FAQ; W = see user guide Section 2.3.5; E = see user guide Section 2.3.6; L = see user's guide Section 5.2; M = mutagen; S = see user guide Section 5; V = volatile; R = RBA applied (see user's guide Section 5.1); c = cancer; n = noncancer; * = where: n SL < 100X c SL; ** = where n SL < 10X c SL; SSL values are based on DAF=1; m = Concentration may exceed ceiling limit (see user's guide Section 5.13); s = concentration may exceed Csat (see user's guide Section 5.12)

Toxicity and Chemical-specific Information															Contaminant		Screening Levels												Protection of Ground Water SSLs		
SFO (mg/kg-day)$^{-1}$	key	IUR (ug/m^3)$^{-1}$	key	RfD$_o$ (mg/kg-day)	key	RfC$_i$ (mg/m^3)	key	volatile	mutagen	GIABS	ABS	Csat (mg/kg)	Analyte	CAS No.	Resident Soil (mg/kg)	key	Industrial Soil (mg/kg)	key	Resident Air (ug/m^3)	key	Industrial Air (ug/m^3)	key	Tapwater (ug/L)	key	MCL (ug/L)	Risk-based SSL (mg/kg)	key	MCL-based SSL (mg/kg)
				1.2E-03	O					1	0.1		Acephate	30560-19-1	7.6E+01	n	9.8E+02	n					2.4E+01	n		5.3E-03	n		
		2.2E-06	I			9.0E-03	I	V		1		1.07E+05	Acetaldehyde	75-07-0	1.1E+01	c**	4.9E+01	c**	1.3E+00	c**	5.6E+00	c**	2.6E+00	c**		5.2E-04	c**		
				2.0E-02	I					1	0.1		Acetochlor	34256-82-1	1.3E+03	n	1.6E+04	n					3.5E+02	n		2.8E-01	n		
				9.0E-01	I	3.1E+01	A	V		1		1.14E+05	Acetone	67-64-1	5.1E+04	n	6.7E+05	nms	3.2E+04	n	1.4E+05	n	1.4E+04	n		2.9E+00	n		
						2.0E-03	X			1	0.1		Acetone Cyanohydrin	75-86-5	2.8E+06	nm	1.2E+07	nm	2.1E+00	n	8.8E+00	n							
						6.0E-02	I	V		1		1.28E+05	Acetonitrile	75-05-8	8.1E+02	n	3.4E+03	n	6.3E+01	n	2.6E+02	n	1.3E+02	n		2.6E-02	n		
				1.0E-01	I			V		1		2.52E+03	Acetophenone	98-86-2	7.8E+03	ns	1.2E+05	nms					1.9E+03	n		5.8E-01	n		
3.8E+00	C	1.3E-03	C							1	0.1		Acetylaminofluorene, 2-	53-96-3	1.4E-01	c	6.0E-01	c	2.2E-03	c	9.4E-03	c	1.6E-02	c		7.2E-05	c		
				5.0E-04	I	2.0E-05	I	V		1		2.27E+04	Acrolein	107-02-8	1.4E-01	n	6.0E-01	n	2.1E-02	n	8.8E-02	n	4.2E-02	n		8.4E-06	n		
5.0E-01	I	1.3E-04	I	2.0E-03	I	6.0E-03	I		M	1	0.1		Acrylamide	79-06-1	2.4E-01	c	4.6E+00	c	1.0E-02	c	1.2E-01	c	5.0E-02	c		1.1E-05	c		
				5.0E-01	I	1.0E-03	I	V		1		1.09E+05	Acrylic Acid	79-10-7	9.9E+01	n	4.2E+02	n	1.0E+00	n	4.4E+00	n	2.1E+00	n		4.2E-04	n		
5.4E-01	I	6.8E-05	I	4.0E-02	A	2.0E-03	I	V		1		1.13E+04	Acrylonitrile	107-13-1	2.5E-01	c*	1.1E+00	c*	4.1E-02	c*	1.8E-01	c*	5.2E-02	c*		1.1E-05	c*		
						6.0E-03	P			1	0.1		Adiponitrile	111-69-3	8.5E+06	nm	3.6E+07	nm	6.3E+00	n	2.6E+01	n							
5.6E-02	C			1.0E-02	I					1	0.1		Alachlor	15972-60-8	9.7E+00	c*	4.1E+01	c					1.1E+00	c	2	8.7E-04	c	1.6E-03
				1.0E-03	I					1	0.1		Aldicarb	116-06-3	6.3E+01	n	8.2E+02	n					2.0E+01	n	3	4.9E-03	n	7.5E-04
				1.0E-03	I					1	0.1		Aldicarb Sulfone	1646-88-4	6.3E+01	n	8.2E+02	n					2.0E+01	n	2	4.4E-03	n	4.4E-04
										1	0.1		Aldicarb sulfoxide	1646-87-3											4			8.8E-04
1.7E+01	I	4.9E-03	I	3.0E-05	I			V		1			Aldrin	309-00-2	3.9E-02	c*	1.8E-01	c	5.7E-04	c	2.5E-03	c	9.2E-04	c		1.5E-04	c		
				5.0E-03	I	1.0E-04	X	V		1		1.11E+05	Allyl Alcohol	107-18-6	3.5E+00	n	1.5E+01	n	1.0E-01	n	4.4E-01	n	2.1E-01	n		4.2E-05	n		
2.1E-02	C	6.0E-06	C			1.0E-03	I	V		1		1.42E+03	Allyl Chloride	107-05-1	7.2E-01	c**	3.2E+00	c**	4.7E-01	c**	2.0E+00	c**	7.3E-01	c**		2.3E-04	c**		
				1.0E+00	P	5.0E-03	P			1			Aluminum	7429-90-5	7.7E+04	n	1.1E+06	nm	5.2E+00	n	2.2E+01	n	2.0E+04	n		3.0E+04	n		
				4.0E-04	I					1			Aluminum Phosphide	20859-73-8	3.1E+01	n	4.7E+02	n					8.0E+00	n					
				9.0E-03	I					1	0.1		Ametryn	834-12-8	5.7E+02	n	7.4E+03	n					1.5E+02	n		1.6E-01	n		
2.1E+01	C	6.0E-03	C							1	0.1		Aminobiphenyl, 4-	92-67-1	2.6E-02	c	1.1E-01	c	4.7E-04	c	2.0E-03	c	3.0E-03	c		1.5E-05	c		
				8.0E-02	P					1	0.1		Aminophenol, m-	591-27-5	5.1E+03	n	6.6E+04	n					1.6E+03	n		6.1E-01	n		
				4.0E-03	X					1	0.1		Aminophenol, o-	95-55-6	2.5E+02	n	3.3E+03	n					7.9E+01	n		3.0E-02	n		
				2.0E-02	P					1	0.1		Aminophenol, p-	123-30-8	1.3E+03	n	1.6E+04	n					4.0E+02	n		1.5E-01	n		
				2.5E-03	I					1	0.1		Amitraz	33089-61-1	1.6E+02	n	2.1E+03	n					8.2E+00	n		4.2E+00	n		
						5.0E-04	I	V		1			Ammonia	7664-41-7					5.2E+02	n	2.2E+03	n							
				2.0E-01	I					1			Ammonium Sulfamate	7773-06-0	1.6E+04	n	2.3E+05	nm					4.0E+03	n					
						3.0E-04	X	V		1		1.37E+04	Amyl Alcohol, tert-	75-85-4	8.2E+01	n	3.4E+02	n	3.1E+00	n	1.3E+01	n	6.3E+00	n		1.3E-03	n		
5.7E-03	I	1.6E-06	C	7.0E-03	P	1.0E-03	I			1	0.1		Aniline	62-53-3	9.5E+01	c**	4.0E+02	c*	1.0E+00	n	4.4E+00	n	1.3E+01	c*		4.6E-03	c*		
4.0E-02	P			2.0E-03	X					1	0.1		Anthraquinone, 9,10-	84-65-1	1.4E+01	c**	5.7E+01	c*					1.4E+00	c*		1.4E-02	c*		
				4.0E-04	I					0.15			Antimony (metallic)	7440-36-0	3.1E+01	n	4.7E+02	n					7.8E+00	n	6	3.5E-01	n	2.7E-01
				5.0E-04	H					0.15			Antimony Pentoxide	1314-60-9	3.9E+01	n	5.8E+02	n					9.7E+00	n					
				4.0E-04	H					0.15			Antimony Tetroxide	1332-81-6	3.1E+01	n	4.7E+02	n					7.8E+00	n					
						2.0E-04	I			0.15			Antimony Trioxide	1309-64-4	2.8E+05	nm	1.2E+06	nm	2.1E+01	n	8.8E+01	n							
1.5E+00	I	4.3E-03	I	3.0E-04	I	1.5E-03	C			1	0.03		Arsenic, Inorganic	7440-38-2	6.8E-01	c*R	3.0E+00	cR	6.5E-04	c*	2.9E-03	c*	5.2E-02	c	10	1.5E-03	c	2.9E-01
				3.5E-06	C	5.0E-05	I			1			Arsine	7784-42-1	2.7E-01	n	4.1E+00	n	5.2E-02	n	2.2E-01	n	7.0E-02	n					
				3.6E-02	O					1	0.1		Asulam	3337-71-1	2.3E+03	n	3.0E+04	n					7.2E+02	n		1.8E-01	n		
2.3E-01	C			3.5E-02	I					1	0.1		Atrazine	1912-24-9	2.4E+00	c	1.0E+01	c					3.0E-01	c	3	2.0E-04	c	1.9E-03
8.8E-01	C	2.5E-04	C							1	0.1		Auramine	492-80-8	5.2E-01	c	2.6E+00	c	1.1E-02	c	4.9E-02	c	6.7E-02	c		6.1E-04	c		
				4.0E-04	I					1	0.1		Avermectin B1	65195-55-3	2.5E+01	n	3.3E+02	n					8.0E+00	n		1.4E+01	n		
				3.0E-03	A	1.0E-02	A			1	0.1		Azinphos-methyl	86-50-0	1.9E+02	n	2.5E+03	n	1.0E+01	n	4.4E+01	n	5.6E+01	n		1.7E-02	n		
1.1E-01	I	3.1E-05	I					V		1			Azobenzene	103-33-3	5.6E+00	c	2.6E+01	c	9.1E-02	c	4.0E-01	c	1.2E-01	c		9.3E-04	c		
				1.0E+00	P	7.0E-05	P			1	0.1		Azodicarbonamide	123-77-3	8.6E+03	n	4.0E+04	n	7.3E-03	n	3.1E-02	n	2.0E+04	n		6.8E+00	n		
				2.0E-01	I	5.0E-04	H			0.07			Barium	7440-39-3	1.5E+04	n	2.2E+05	nm	5.2E-01	n	2.2E+00	n	3.8E+03	n	2000	1.6E+02	n	8.2E+01
				5.0E-03	O			V		1			Benfluralin	1861-40-1	3.9E+02	n	5.8E+03	n					2.8E+01	n		9.4E-01	n		
				5.0E-02	I					1	0.1		Benomyl	17804-35-2	3.2E+03	n	4.1E+04	n					9.7E+02	n		8.5E-01	n		
				2.0E-01	I					1	0.1		Bensulfuron-methyl	83055-99-6	1.3E+04	n	1.6E+05	nm					3.9E+03	n		1.0E+00	n		
				3.0E-02	I					1	0.1		Bentazon	25057-89-0	1.9E+03	n	2.5E+04	n					5.7E+02	n		1.2E-01	n		
4.0E-03	P			1.0E-01	I			V		1		1.16E+03	Benzaldehyde	100-52-7	1.7E+02	c*	8.2E+02	c					1.9E+01	c		4.1E-03	c		
5.5E-02	I	7.8E-06	I	4.0E-03	I	3.0E-02	I	V		1		1.82E+03	Benzene	71-43-2	1.2E+00	c*	5.1E+00	c*	3.6E-01	c*	1.6E+00	c*	4.6E-01	c*	5	2.3E-04	c*	2.6E-03
1.0E-01	X			3.0E-04	X					1	0.1		Benzenediamine-2-methyl sulfate, 1,4-	6369-59-1	5.4E+00	c**	2.3E+01	c*					7.8E-01	c**		2.2E-04	c**		
				1.0E-03	P			V		1		1.26E+03	Benzenethiol	108-98-5	7.8E+01	n	1.2E+03	n					1.7E+01	n		1.1E-02	n		
2.3E+02	I	6.9E-02	I	3.0E-03	I				M	1	0.1		Benzidine	92-87-5	5.3E-04	c	1.0E-02	c	1.5E-05	c	1.8E-04	c	1.1E-04	c		2.8E-07	c		
				4.0E+00	I					1	0.1		Benzoic Acid	65-85-0	2.5E+05	nm	3.3E+06	nm					7.5E+04	n		1.5E+01	n		
1.3E+01	I							V		1		3.24E+02	Benzotrichloride	98-07-7	5.3E-02	c	2.5E-01	c					3.0E-03	c		6.6E-06	c		
				1.0E-01	P					1	0.1		Benzyl Alcohol	100-51-6	6.3E+03	n	8.2E+04	n					2.0E+03	n		4.8E-01	n		
1.7E-01	I	4.9E-05	C	2.0E-03	P	1.0E-03	P	V		1		1.46E+03	Benzyl Chloride	100-44-7	1.1E+00	c*	4.8E+00	c*	5.7E-02	c*	2.5E-01	c*	8.9E-02	c*		9.8E-05	c*		
		2.4E-03	I	2.0E-03	I	8.0E-06	I			0.007			Beryllium and compounds	7440-41-7	1.6E+02	n	2.3E+03	n	1.2E-03	c*	5.1E-03	c*	2.5E+01	n	4	1.9E+01	n	3.2E+00
				9.0E-03	P					1	0.1		Bifenox	42576-02-3	5.7E+02	n	7.4E+03	n					1.0E+02	n		7.6E-01	n		
				1.5E-02	I					1	0.1		Biphenthrin	82657-04-3	9.5E+02	n	1.2E+04	n					3.0E+02	n		1.4E+03	n		
8.0E-03	I			5.0E-01	I	4.0E-04	X	V		1			Biphenyl, 1,1'-	92-52-4	4.7E+01	n	2.0E+02	n	4.2E-01	n	1.8E+00	n	8.3E-01	n		8.7E-03	n		
				4.0E-02	I			V		1		1.02E+03	Bis(2-chloro-1-methylethyl) ether	108-60-1	3.1E+03	ns	4.7E+04	ns					7.1E+02	n		2.6E-01	n		
				3.0E-03	I					1	0.1		Bis(2-chloroethoxy)methane	111-91-1	1.9E+02	n	2.5E+03	n					5.9E+01	n		1.3E-02	n		
1.1E+00	I	3.3E-04	I					V		1		5.05E+03	Bis(2-chloroethyl)ether	111-44-4	2.3E-01	c	1.0E+00	c	8.5E-03	c	3.7E-02	c	1.4E-02	c		3.6E-06	c		
2.2E+02	I	6.2E-02						V		1		4.22E+03	Bis(chloromethyl)ether	542-88-1	8.3E-05	c	3.6E-04	c	4.5E-05	c	2.0E-04	c	7.2E-05	c		1.7E-08	c		
				5.0E-02	I					1	0.1		Bisphenol A	80-05-7	3.2E+03	n	4.1E+04	n					7.7E+02	n		5.8E+01	n		
				2.0E-02	I	2.0E-02	H			1			Boron And Borates Only	7440-42-8	1.6E+04	n	2.3E+05	nm	2.1E+01	n	8.8E+01	n	4.0E+03	n		1.3E+01	n		
				2.0E-02	P	2.0E-02	P	V		1			Boron Trichloride	10294-34-5	1.6E+05	nm	2.3E+06	nm	2.1E+01	n	8.8E+01	n	4.2E+01	n					

The RSL Table doesn't tell you the potentially harmful effect of a chemical.

For that, you need to go to IRIS itself.

I.A.1. Oral RfD Summary

Screenshot from IRIS, for daminozide (aka Alar)

Critical Effect	Experimental Doses*	UF	MF	RfD
3-Generation Reproduction Rat Study Uniroyal Chemical, 1966	NOEL: 300 ppm (15 mg/kg/day) LEL: none	100	1	1.5E-1 mg/kg/day

*Conversion Factors -- 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

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Uniroyal Chemical, 1966				

Take due note

*Conversion Factors -- 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

I.A.1. Oral RfD Summary

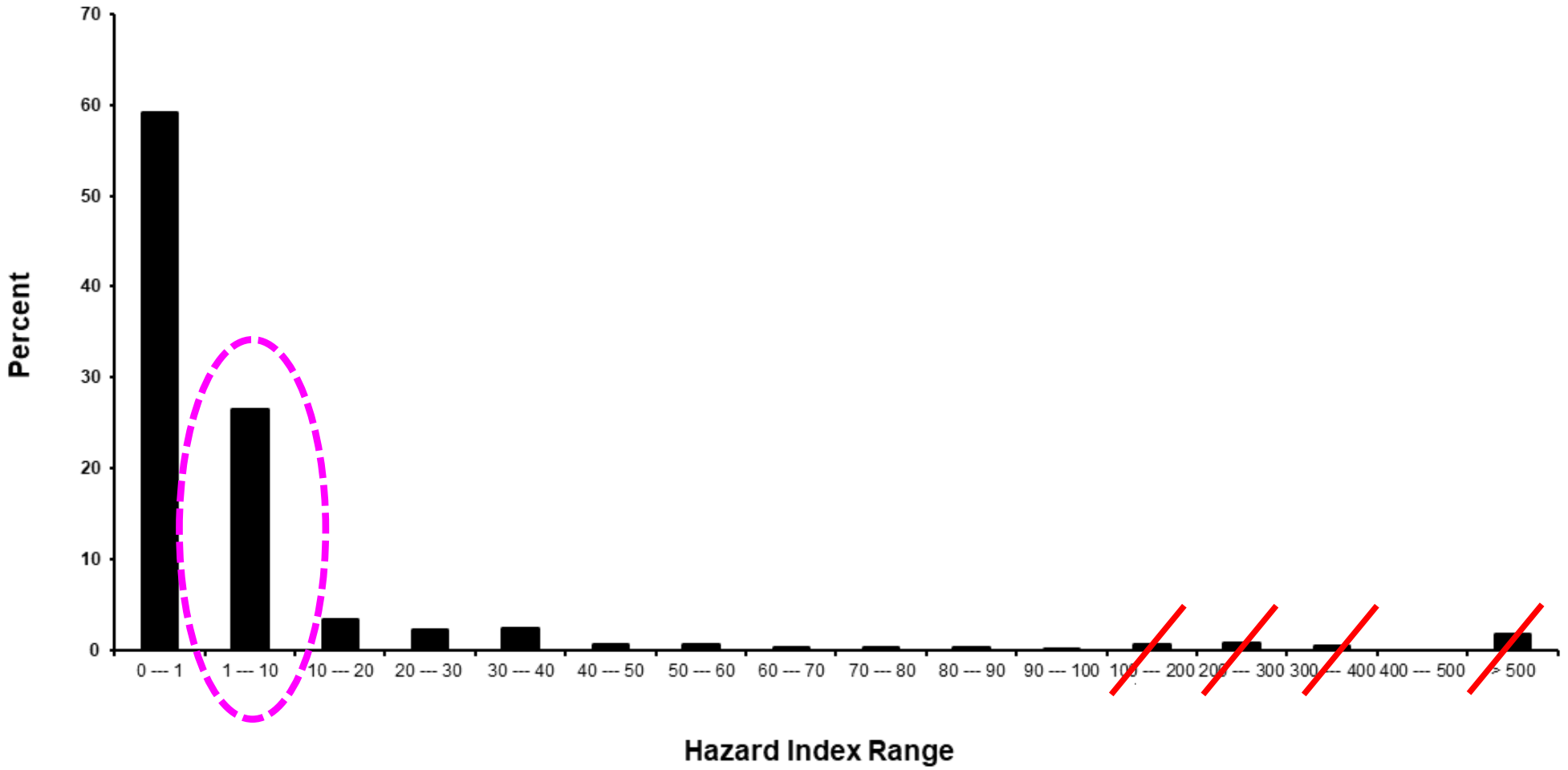
Screenshot from From IRIS, for 1,2-Dichlorobenzene

Critical Effect	Experimental Doses*	UF	MF	RfD
No adverse effects observed	NOAEL: 120 mg/kg/day (adjusted to 85.7 mg/kg/day)	1000	1	9E-2 mg/kg/day
2-Year Rat Study, Oral Exposure (gavage)	LOAEL: None			
NTP, 1985				

Now suppose you calculate an intake of 0.31 mg/kg/d for the site worker.

Your HQ for the site worker would be: 0.31 / 0.09 = **3.44** ☹

HQ (HI) Magnitudes (reflecting 1,000 or so Superfund RODs)



Source: Tannenbaum et al., 2003. Human and Ecological Risk Assessment, Volume 9 (1): 387-401. .

A curious statistic of interest:

- Some **7%** of chemicals with oral RfDs, despite showing “no effect” or “no adverse effect” as the critical effect in IRIS -- seemingly an open indication that chemicals are not linked with adverse responses at the doses tested -- had an RfD provided nevertheless!

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Recognition of Adverse and Nonadverse Effects in Toxicity Studies

RICHARD W. LEWIS,[1] RICHARD BILLINGTON,[2] ERIC DEBRYUNE,[3] ARMIN GAMER,[4] B. LANG, AND FRANCIS CARPANINI[6]

[1]*Syngenta CTL, Health Assessment and Environmental Safety, Alderley Park, Cheshire UK SK10 4TJ*
[2]*Dow AgroScience, Oxford UK*
[3]*Aventis Crop Protection, Sophia Antipolis, France*
[4]*BASF AG, Ludwigshaven, Germany*
[5] *Syngenta AG, Basel, Switzerland, John Van Miller, Union Carbide, Danbury, CT, USA, and*
[6]*ECETOC, Brussels, Belgium*

ABSTRACT

One of the most important quantitative outputs from toxicity studies is identification of the highest exposure level (dose or concentration) that does not cause treatment related effects that could be considered relevant to human health risk assessment. A review of regulatory and other scientific literature and of current practices has revealed a lack of consistency in definition and application of frequently used terms such as No Observed Effect Level (NOEL), No Observed Adverse Effect Level (NOAEL), adverse effect, biologically significant effect, or toxicologically significant effect. Moreover, no coherent criteria were found that could be used to guide consistent interpretation of toxicity studies, including the recognition and differentiation between adverse and nonadverse effects. This presentation will address these issues identified first by proposing a standard set of definitions for key terms such as NOEL and NOAEL that are frequently used to describe the overall outcome of a toxicity study. Second, a coherent framework is outlined that can assist the toxicologist in arriving at consistent study interpretation. This structured process involves two main steps. In the first, the toxicologist must decide whether differences from control values are treatment related or if they are chance deviations. In the second step, only those differences judged to be effects are further evaluated in order to discriminate between those that are adverse and those that are not. For each step, criteria are described that can be used to make consistent judgments. In differentiating an effect from a chance finding, consideration is given inter alia to dose response, spurious measurements in individual parameters, the precision of the measurement under evaluation, ranges of natural variation and the overall biological plausibility of the observation. In discriminating between the adverse and the non-adverse effect consideration is given to: whether the effect is an adaptive response, whether it is transient, the magnitude of the effect, its association with effects in other related endpoints, whether it is a precursor to a more significant effect, whether it has an effect on the overall function of the organism, whether it is a specific effect on an organ or organ system or secondary to general toxicity or whether the effect is a predictable consequence of the experimental model. In interpreting complex studies it is recognised that a weight of the evidence approach, combining the criteria outlined here to reach an overall judgment, is the optimal way of applying the process. It is believed that the use of such a scheme will help to improve the consistency of study interpretation that is the foundation of hazard and risk assessment.

Keywords. Toxicity; adverse effects; nonadverse effects; NOEL; NOAEL; hazard identification.

What about oral RfDs that *do* have listed effects?

"An adverse effect is a biochemical, morphological, or physiological change (in response to a stimulus) that either singly or in combination adversely affects **the performance** of the whole organism or reduces the organism's ability to respond to an additional environmental challenge." (Lewis et al., 2002)

Sorry to say, but no one's really implemented or applied the "**adversity**" definition since then.

IMHO, the 2019 Tannenbaum and Comaty paper makes big inroads for this critically important topic that everyone else seems to be ignoring.

Let's look at some common and not-so-common oral RfD critical effects in IRIS

- hemosiderin deposition in the liver
- presence of Heinz bodies
- renal tubule epithelial vacuolation
- increased retinal folds
- ocular exudate
- vacuolization of zona fasciculata in the cortex
- liver toxicity

Q. Is there something '*bad*' about any of these? If so, what is it?

A critical effects 'check-list' (ex. *hemosiderin depos.*)

Does an animal with this condition:

- Posture/locomote normally?
- Socialize normally?
- Lose/gain weight more than it should?
- Sire/bear as many as do controls?
- Learn/retain information (maze run) normally?
- Live as long as controls?
- Hemorrhage unexpectedly?
- Develop infections when others do not?

What is it that an animal with hemosiderin deposition in the liver can't do?

Is hemosiderin deposition in the liver **bad**?

- for the rat?

Story time: a classic tox study supporting HHRA is done . .

- A highly controlled study: **same** a) species, b) strain, c) animal supplier, d) animal arrival day, e) animal weights, f) quarantining, g) cages/bedding/ bottles/water/toys, h) temperature, humidity, and lighting. Animals randomized into treatments.
- A single variable - one group gets the chemical ; the other either gets nothing or receives the vehicle).
- After the dosing phase, animals are euthanized, organ-to-b.w. ratios are computed, enzymes and hormones are analyzed, histological examination of all major organs/tissues.
- The only statistical difference observed? The dosed group had spleens that were 4.5% larger than those of controls.
- **Is there sufficient information to support the development of an oral RfD?**

ABSOLUTELY NOT!

A 4.5% enlarged spleen could be *beneficial* for the animal, though. Think about it …

At a BARE BONES MINIMUM, in order to proceed with RfD development, one must know that an observed effect is **bad / adverse / deleterious in the test animal!**

With the way we test presently, we can't know this!

Beware of what I call “guilt by association”.

You cannot tell if a test animal . . .

- postures/locomotes normally,
- socializes normally,
- loses or gains weight unlike controls,
- sires or bears fewer than do controls,
- learns/retains information normally,
- has compromised longevity,
- hemorrhages unexpectedly, or
- develops more infections than do controls . . . **if you euthanize it!**

Desperately needed to repair non-cancer assessment

"Second-order toxicology", aka "*toxicology's missing link*"

First-order toxicology: includes all those information types that come to mind when you hear: 'toxicology' or 'toxicology study'.

- establishing the principal organ/tissue affected;
- threshold-for-effect;
- shape of the dose-response curve;
- differential response (male/female; fed/fasted, etc.);
- mode/mechanism of action;
- pharmacokinetics, etc., etc.

Second-order toxicology pertains to just one additional toxicological tasking --

- a very basic one;
- one that hasn't yet been tackled;
- one that involves a fair amount of work to secure;
- one that can be supplied if the risk assessors and toxicologists work together!

Second-order toxicology tells you
if a toxicological effect is ***BAD*** for a receptor.

Important: It's probably **not** because second-order toxicology is challenging and elusive to ascertain that we don't have it.

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Letter to the Editor

A FERVENT PLEA FOR SECOND-ORDER TOXICOLOGY

Readers of peer-reviewed toxicology journals of distinction, such as *Environmental Toxicology and Chemistry*, are well-versed in the plethora of information that is commonly brought forward by what may be termed "conventional" toxicology studies. These studies may, among other things, furnish proof that a chemical is indeed toxic, pinpoint the organ or organ system that is affected, indicate threshold doses for effect, map out the dose–response curve, determine if effects might be reversible, elucidate a chemical's mode of action, and document a chemical's pharmacokinetics. As scholarly and authoritative as

receptor, perhaps a fox, is ingesting chemical X at a rate 10 times that at which seminiferous tubules become narrowed. Disregarding for the moment the fact that hazard quotients are not actual risk measures [4], the assessor would conclude that the fox is at risk for reproductive effects. The assessor would, however, be quite wrong with his or her conclusion and certainly premature in having arrived at one. Though the parent study from which the TRV was derived may have unambiguously established that chemical X, for a certain dosing regimen, produces narrowed seminiferous tubules, it was never estab-

The "Truly Adverse Dose" ("TAD") concept . . .

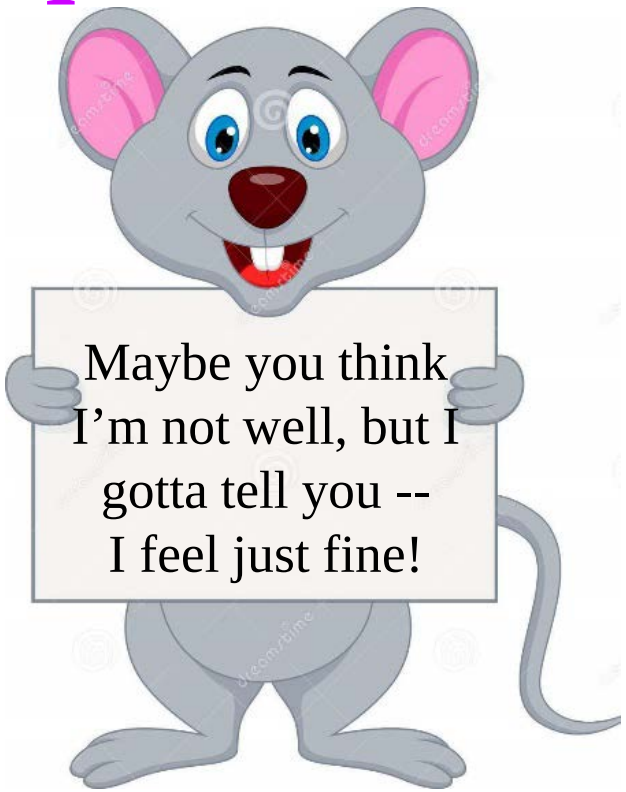
- Conduct (repeat) a 'traditional' rodent study.
- Identify/verify the (sublethal) 'effect of concern' (say, *renal tubulular epithelial vacuolization* as is reported for chorothalonil in IRIS; **from 1970**).
- Run the experiment again using double the number of animals.
- At the end of the dosing phase, euthanize half of the animals - to verify again, that the effect happened.
- Maintain the rest of the animals until their natural death. Along the way, test (relative to controls) for overall health, growth, longevity, reproductive capability, and whatever else is seemingly important.
  TEST FOR PERFORMANCE!
- If no vital biological functions are compromised, the earlier observed 'critical effect' is inconsequential and harmless. No RfD needed here.

More on the TAD concept . . .

For an improved noncancer assessment scheme, we propose replacing the present design that seeks to know if supposed safe doses are exceeded, with . . . one that looks to see if unquestionably (truly) adverse doses are approached.

For this new arrangement, **the RfD** (i.e., the supposed safe dose) **would be replaced** with what we are terming the **truly adverse dose** (TAD), one for which second-order toxicology information (corresponding to the expression of serious health conditions) exists.

Who's got questions or comments?



The opinions or assertions contained herein are the views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Grandchild #10! (a ‘he’)

Born last Friday.

Too young to attend the workshop. ☹