TOXICITY EVALUATION – 2

Determination of Threshold Level



Was is dast nit gifft ist? Alle ding sind gifft/ und nicht on gifft/Allein die dosis macht ein ding kein gifft ist.

What is there that is not poison? All things are poison and nothing (is) without poison. Solely, the dose determines that a thing is not a poison.

Paracelsus (1493-1541)



Solely, the dose determines that a thing is not a poison (*Paracelsus* 1493-1541)

THE THRESHOLD PRINCIPLE "Ngono yo ngono ning ojo ngono"



Determination of Threshold



WHAT IS A Threshold?

BIOLOGICAL DEFINITION

The dose below which the organism does not suffer from any (adverse) effects from the compound considered.

EXPERIMENTAL DEFINITION

The dose below which no effects are observed

MATHEMATICAL DEFINITION

The dose below which the response is zero, and above which it is non-zero



Individuals' Thresholds



Population Threshold





DETERMINATION OF NO EFFECT

No Observed Effect Concentration (NOEC) No Observed Adverse Effect Level (NOAEL) No Effect Level (NEL)

Can be obtained from ANOVA (*analysis of variance*) of the dose response data involving a control treatment.....followed by a post hoc test e.g. THE DUNNETT'S TEST



TYPICAL DATA OF NO EFFECT DETERMINATION

Example: a toxicity experiment using hamster (dietary exposure of Cd - 4 weeks)

Treatment*	Body Weight (g)	Average
Control	55.1, 55.2, 55.3, 54.9, 58.3	X
Cd-1 ppm	54.1, 54.2, 55.4, 53.9, 56.3	
Cd-2 ppm	49.1, 47.2, 45.3, 42.9, 47.3	$\mathbb{Z}_2 > 0$
Cd-3 ppm	38.1, 37.2, 37.3, 36.9, 38.3	$\overline{X_3}$ V
Cd-4 ppm	24.1, 25.2, 25.3, 34.9, 29.3	

*) Cd-1 to 4 ppm = cadmium concentration in the diet (1 ppm to 4 ppm)

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	4	0	54.9							
	5	0	58.3							
	6	1	54.1							
	7	1	54.2							
	8	1	55.4							
	9	1	53.9							
	10	1	56.3							
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	14	2	42.9							
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	18	3	37.3							
	19	3	36.9							
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	conc	weight	One-Way ANOVA: Post Hoc Multiple Comparisons
1	0	55.1	
2	0	55.1	Equal Variances Assumed
3	0	55.1	🗖 LSD 🔲 S-N-K 📄 Waller-Duncan
4	0	54.9	Bonferroni Tukey Type I/Type II Error Ratio: 100
5	0	58.(Sidak Tukey's-b Dunnett
6	1	54.1	Scherre Duncan Control Category: Last
7	1	54.1	B-E-G-W 0 Gabriel C 2-sided C 2 Control C > Control
8	1	55.4	
9	1	53.9	Equal Variances Not Assumed
10	1	56.(🗖 Tamhane's T2 🔽 Dunnett's T3 🔲 Games-Howell 🔲 Dunnett's C
11	2	49.1	
12	2	47.1	Significance level: .05
13	2	45.:	Continue Cancel Help
14	2	42.9	
15	2	47.3	
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Oneway

Descriptives

WEIGHT

						95% Confidence Interval for			
						Me	an		
		N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum
•	0	5	55.760	1.428	.638	53.987	57.533	54.9	58.3
	1	5	54.780	1.033	.462	53.497	56.063	53.9	56.3
	2	5	46.360	2.355	1.053	43.435	49.285	42.9	49.1
	3	5	37.560	.607	.271	36.807	38.313	36.9	38.3
	4	5	27.760	4.454	1.992	22.230	33.290	24.1	34.9
	Total	25	44.444	11.062	2.212	39.878	49.010	24.1	58.3

ANOVA

WEIGHT

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2821.506	4	705.376	122.211	.000
Within Groups	115.436	20	5.772		
Total	2936.942	24			



Post Hoc Tests

Multiple Comparisons

Dependent Variable: WEIGHT

Dunnett T3

		Mean Difference			95% Confide	ence Interval
(I) CONC	(J) CONC	(I-J)	Std. Error	Sig.	Lower Bound	Upper Bound
0	1	.980	1.519	.875	-2.018	3.978
	2	9.400*	1.519	.001	4.713	14.087
	3	18.200*	1.519	.000	15.209	21.191
	4	28.000*	1.519	.000	18.981	37.019
1	0	980	1.519	.875	-3.978	2.018
	2	8.420*	1.519	.005	3.461	13.379
	3	17.220*	1.519	.000	15.073	19.367
	4	27.020*	1.519	.001	17.171	36.869
2	0	-9.400*	1.519	.001	-14.087	-4.713
	1	-8.420*	1.519	.005	-13.379	-3.461
	3	8.800*	1.519	.003	4.110	13.490
	4	18.600*	1.519	.001	9.570	27.630
3	0	-18.200*	1.519	.000	-21.191	-15.209
	1	-17.220*	1.519	.000	-19.367	-15.073
	2	-8.800*	1.519	.003	-13.490	-4.110
	4	9.800*	1.519	.048	.117	19.483
4	0	-28.000*	1.519	.000	-37.019	-18.981
	1	-27.020*	1.519	.001	-36.869	-17.171
	2	-18.600*	1.519	.001	-27.630	-9.570
	3	-9.800*	1.519	.048	-19.483	117



* The mean difference is significant at the .05 level.

 $\begin{array}{|c|c|c|c|} & & & \boxtimes_{1} \\ \hline \boxtimes_{0} & & & \boxtimes_{2^{**}} \\ \hline \boxtimes_{0} & & & \boxtimes_{3^{**}} \\ \hline \boxtimes_{0} & & & \boxtimes_{4^{**}} \end{array}$

NOEC = 1 ppm



NOAEL as a foundation of food safety measures: ADI & MTWI



ADI = acceptable daily intake

MTWI = maximum tolerable weekly intake

ADI = NOAEL/100 -----> Safety Factor



ADI

the maximum amount of toxic substance that can be consumed by human in one day (mg per kg body weight) without any impact on health

 $\mathsf{MTWI} = \mathsf{7} \mathsf{X} \mathsf{ADI}$

MTWI

the maximum amount of toxic substances that can be consumed by human in one week (mg per kg body weight) without any impact on health



Toxicity profile

- Websites:
 - TOXNET
 - ASTDR
 - HIGHWIRE (portal of free journals, Stanford University)
 - PROQUEST

NAME AND DESCRIPTION OF THE TOXICANT PHYSICO-CHEMICAL PROPERTIES TOXICITY ON HUMAN/ANIMALS LC50, NOEC