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.

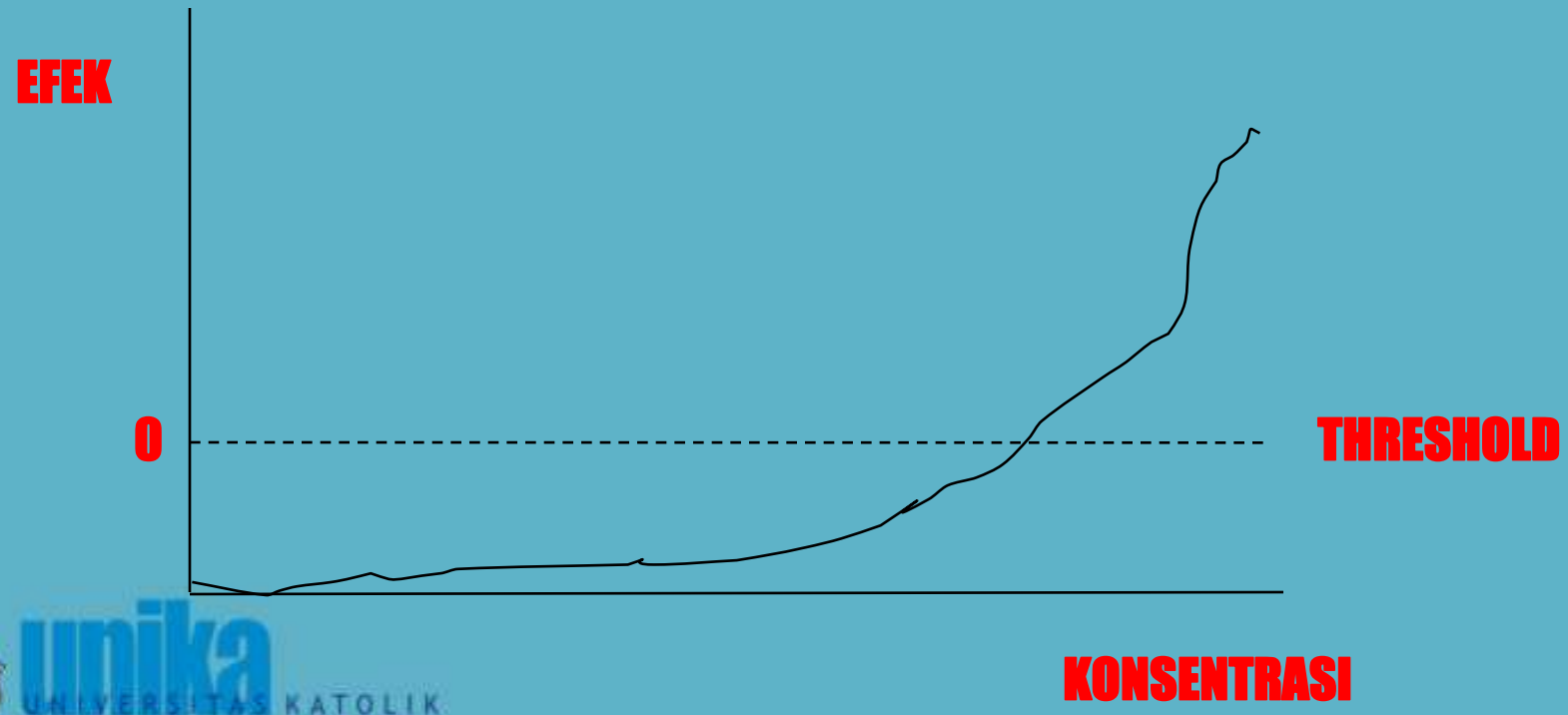
What is there that is not poison? All things are poison and nothing (is) without poison. Solely, the dose determines that a thing is not a poison.

***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"



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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.

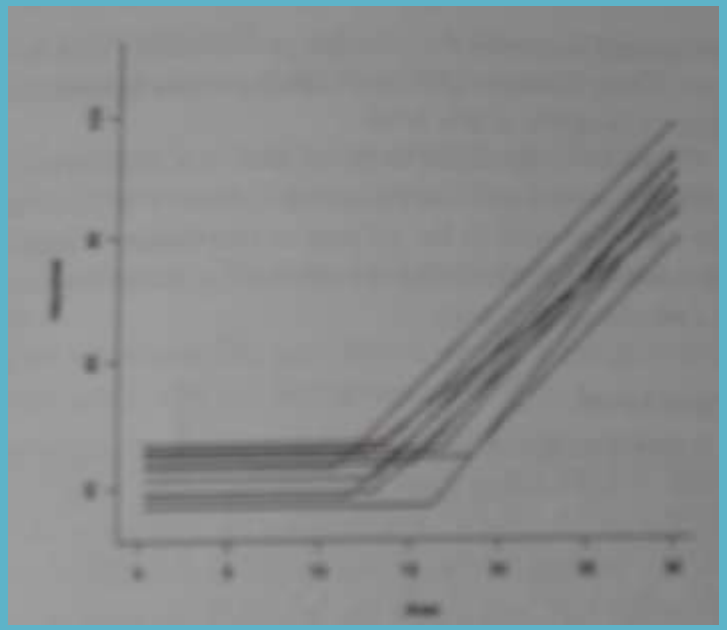
- **EXPERIMENTAL DEFINITION**

  The dose below which no effects are observed

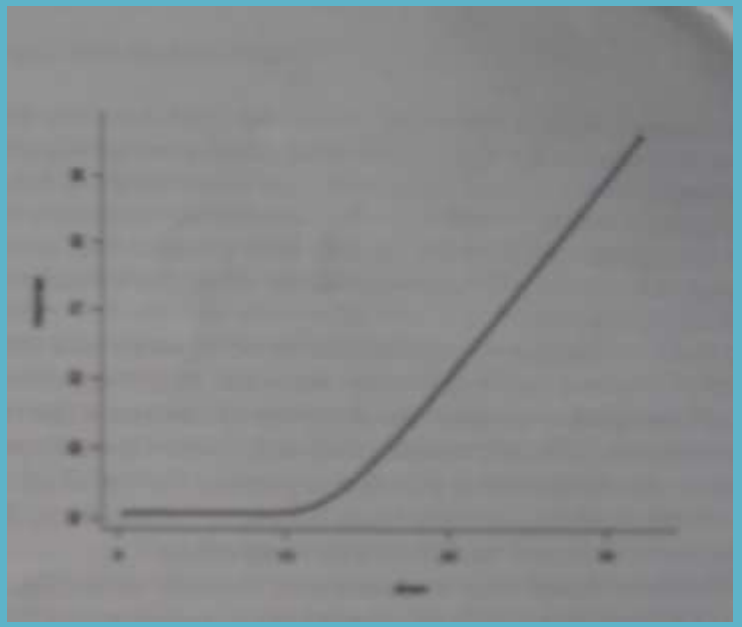
- **MATHEMATICAL DEFINITION**

  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	$\bar{x}_0$
Cd-1 ppm	54.1, 54.2, 55.4, 53.9, 56.3	$\bar{x}_1$
Cd-2 ppm	49.1, 47.2, 45.3, 42.9, 47.3	$\bar{x}_2$
Cd-3 ppm	38.1, 37.2, 37.3, 36.9, 38.3	$\bar{x}_3$
Cd-4 ppm	24.1, 25.2, 25.3, 34.9, 29.3	$\bar{x}_4$

ANOVA

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

Untitled - SPSS Data Editor

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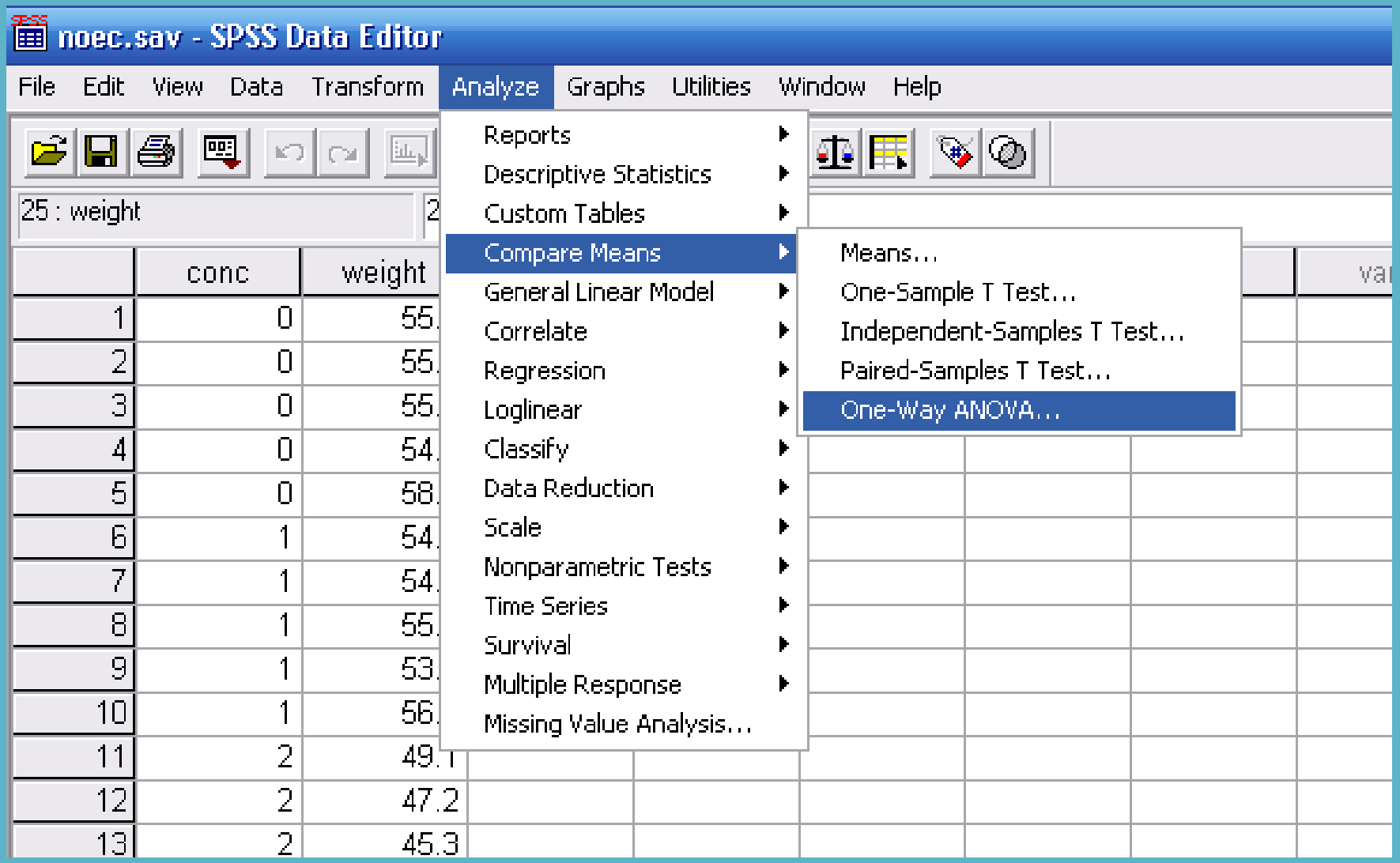
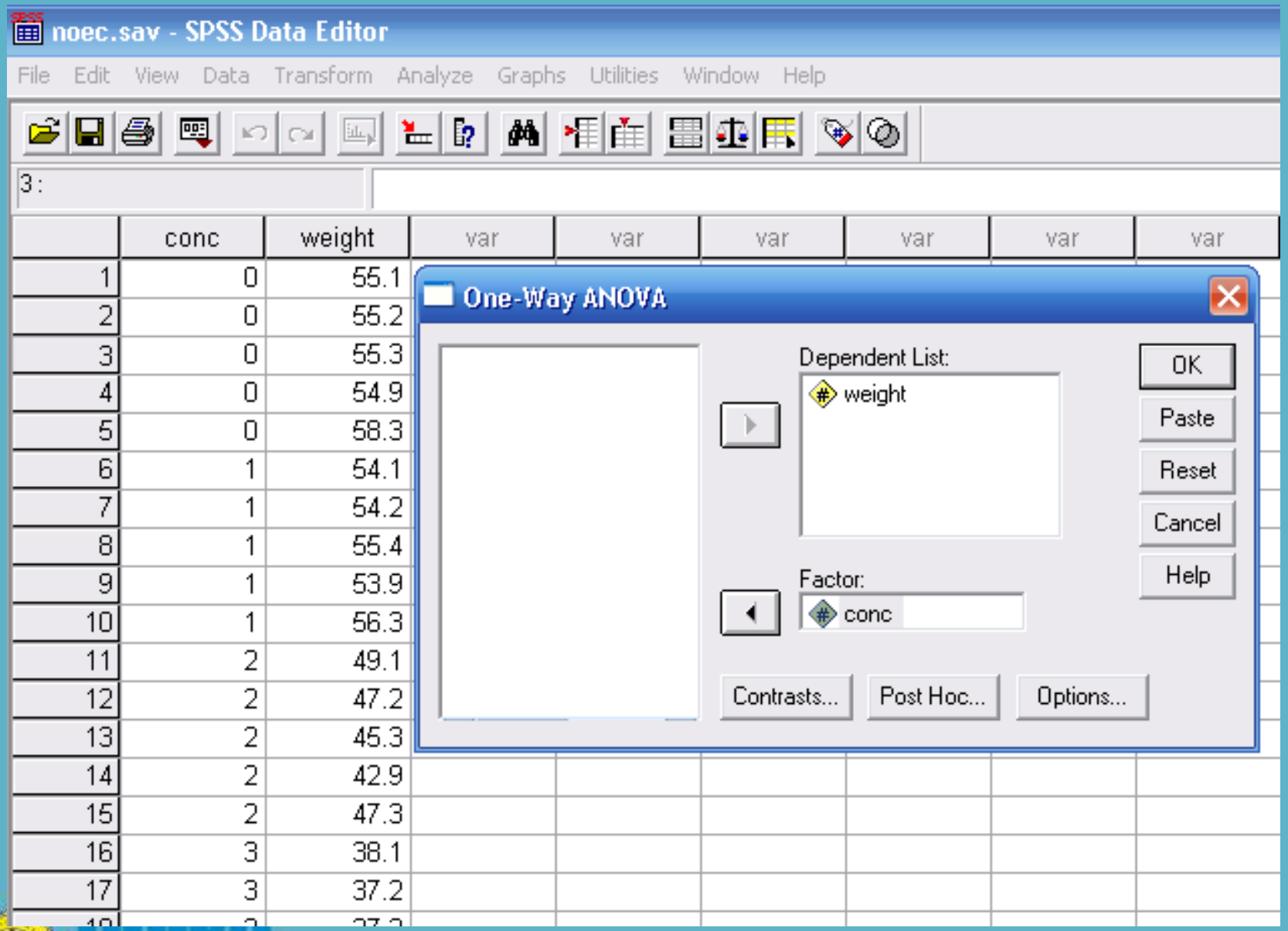
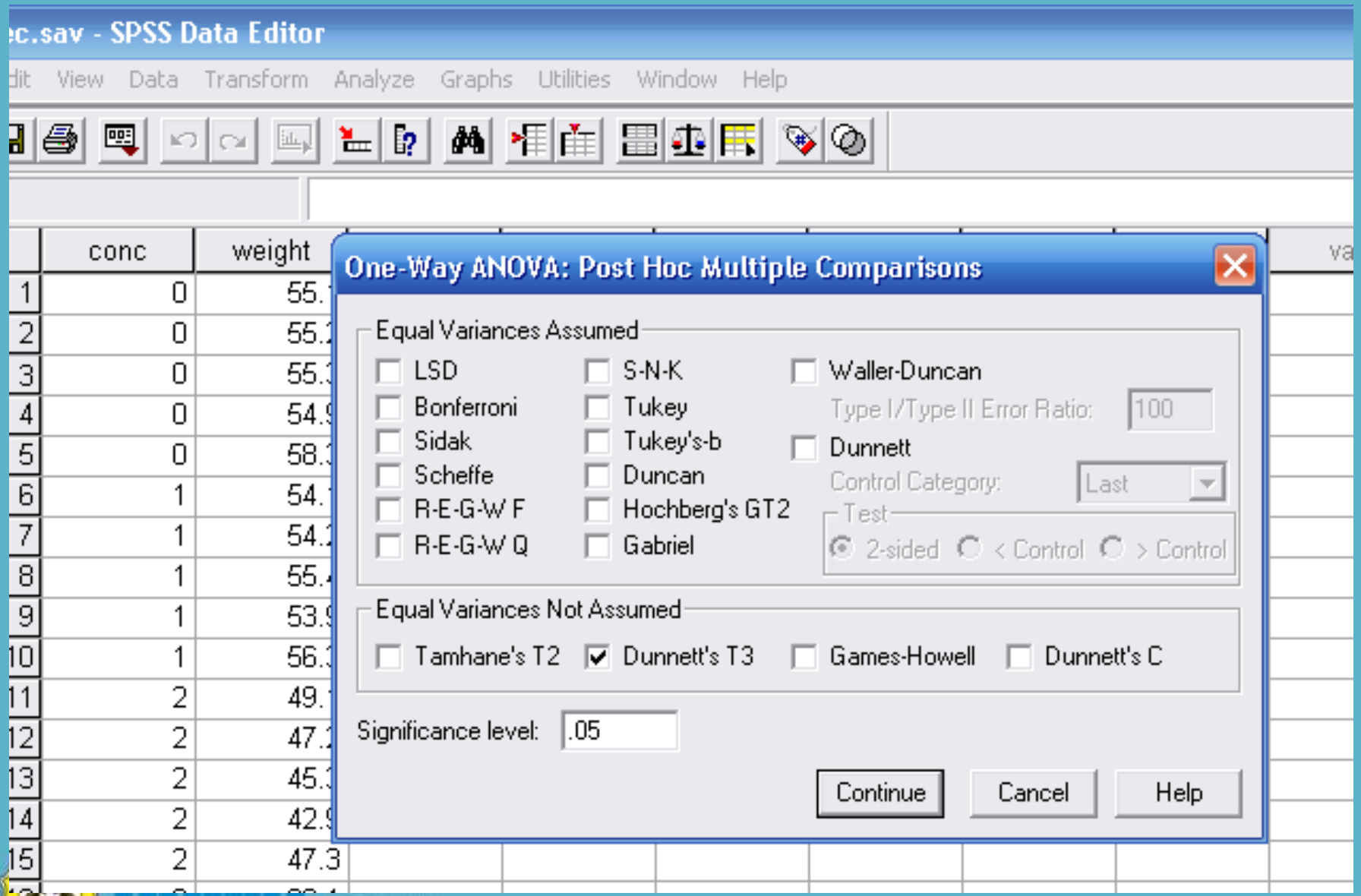
25 : weight 29.3

	conc	weight	var	var	var	var	var	var
1	0	55.1						
2	0	55.2						
3	0	55.3						
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						
11	2	49.1						
12	2	47.2						
13	2	45.3						
14	2	42.9						
15	2	47.3						
16	3	38.1						
17	3	37.2						
18	3	37.3						
19	3	36.9						
20	3	38.3						
21	4	24.1						
22	4	25.2						
23	4	25.3						
24	4	34.9						
25	4	29.3						







Output1 - SPSS Viewer

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Oneway

Descriptives

WEIGHT

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
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			

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Post Hoc Tests

Multiple Comparisons

Dependent Variable: WEIGHT

Dunnett T3

(I) CONC	(J) CONC	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					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.

$\boxtimes_0$ vs $\boxtimes_1$

$\boxtimes_0$ vs $\boxtimes_{2**}$

$\boxtimes_0$ vs $\boxtimes_{3**}$

$\boxtimes_0$ vs $\boxtimes_{4**}$

NOEC = 1 ppm

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

NOAEL (exp. animal) → ADI (human) → MTWI (human)

ADI = acceptable daily intake

MTWI = maximum tolerable weekly intake

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

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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

$$MTWI = 7 \times ADI$$

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