الكلية	الصيدلة
القسم	الادوية والسموم
المادة باللغة الانجليزية	Practical Toxicology
المادة باللغة العربية	سموم سريري
المرحلة الدراسية	الخامسة
اسم التدريسي	م.م.مصطفى عدنان عبد
عنوان المحاضرة باللغة الانجليزية	Acute toxicity study determination of Lethal dose 50
عنوان المحاضرة باللغة العربية	دراسة السمية الحادة لتحديد نصف الجرعة المميتة
رقم المحاضرة	4
المصادر والمراجع	*Guidelines for the Testing of Chemicals – Section 4: Health Effects. Test No. 425: Acute Oral Toxicity – Up-and-Down Procedure.* OECD Publishing, Paris, 2022.
	Guidelines for the Testing of Chemicals, Test No. 420: Acute Oral Toxicity – Fixed Dose Procedure. OECD, 2017.
	"A Simplified Method of Evaluating Dose-Effect Experiments." *Journal of Pharmacology and Experimental Therapeutics,* 1949, 96(2): 99–113.

محتوى المحاضرة

Introduction:

Xenobiotics-: They are substances which not enter any biological processes or used as source of energy or nutrition, so they consider as foreign compounds, (e.g.) drugs, heavy metals, Insecticides

Toxic effect-: Damaged effect to certain biological, system or process caused by poison or drug at high doses.

Type of toxicity

<u>1- Acute toxicity</u>: sudden violent syndrome caused by single large dose of toxicant with high mortality and sever toxic symptoms.

2- Sub acute toxicity: repeated large toxic doses for a period less than one month, with sever toxic symptoms and some mortality.

3- Sub chronic toxicity: repeated moderated to low toxic doses for a period less than three months with moderated toxic symptoms.

4- Chronic toxicity: Long term condition by repeated small doses for a period more than three months with or without any toxicity symptoms, its used to study carcinogenicity and accumulation.

Principle of LD50 or TD50 test

1-Different methods may be used to do so, large number of lab animals must be used (40-50) divided into at least five doses.

2-The doses chose according to pilot study result.

3-Mice, rat is the most recommended lab animal, sometime rabbit, Guinea pig.

4- The intended route of administration is the most common used route (drug or additive).

LD50 Determination Methods:

I-LITCHFIELD AND WILCOKSON:

2-NORMAL EQUIVALENT DEVIATION:

3-PROBIT METHOD:

4-UP & DOWN METHOD:

UP & DOWN (staircase) method occur by two way:

1. **MAIN TEST :**
2. **This test must be performed in situations when there is little or no information about material toxicity, or in which the test material is expected to be toxic.**
3. **A single ordered dose 175 mg/kg must choose because it is likely to be below the LD 50 of most chemicals.**

4. **If the animal survives, the dose for the next animal is increased by a factor of (3.2 times) the original dose ; if it dies, the dose for the next animal is decreased by a similar dose progression.**

2. LIMIT TEST :

- **The limit test is primarily used in situation where the experiment has information indicating that test material is likely to be non-toxic . Such as food additive.**
- **Its a serial test that uses a maximum of 5 animals. A test dose of 5 g or ml /kg used, after overnight fasting for rats.**
- **For this reason, it called the "limit test." In general, 5 gm or 5 ml of the test substance/kg is the practical upper limit for test material that can be administered in one oral gavage dose to a rodent.**
- **Test animals should be observed closely for up to 14 days; symptoms of toxicity and recovery should be noted.**
- **Gross and histopathological examination of the test animals at the end of the study may help identify toxic effects on target organs.**
- **<u>If no animals die as a result of this dose, there is no need to test higher dosages.</u>**
- **The acute toxicity of the compound can then be expressed as being greater than 5 g or ml/kg body weight of the test animal.**

General Procedure:

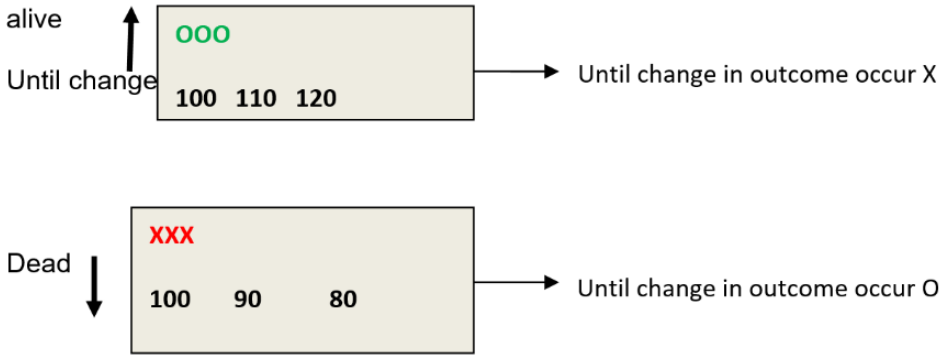
1-Dose given in intended route individually to lab animal.

2-The response recording as two phases.

3-Constant increase in dose .

4- In case alive response (O) or no response within 24 hr., the increase or decrease must be 10-20% of initial dose.

5-The outcome of dosing is dead or alive



6-Constant phase usually ended with opposite response outcome OOOX or XXO.

7-Three shots of variable phase depend on the increasing or decreasing the dose opposite to the outcomes occur at the same dosing ratio.

e.g. X **OXO** or O **XXO** variable phase.

8-Write the results as symbol and calculate LD_{50} according to up and down following equation.

e.g. 1 **100 110 120 130 120 130 120**
O OO X O X O

e.g 2 **100 90 80 70 80 70 60**
O X X O X XX

$LD_{50} = xf + Kd$

Xf = the last dose

K= factor from the table according to constant and

Variable.

d= differences between doses used.

Measurement of LD50 (Dixon, 1980)

Second part of serial	+ K : Tests serial				
	O	OO	OOO	OOOO	
XOOO	-0.157	-0.154	-0.154	-0.154	OXXX
XOOX	0.878	-0.861	-0.860	-0.860	OXXO
XOXO	0.701	0.737	0.741	0.741	OXOX
XOXX	0.084	0.169	0.181	0.186	OXOO
XXOO	0.305	0.372	0.380	0.381	OOXX
XXOX	-0.305	-0.169	-0.144	-0.142	OOXO
XXXO	1.288	1.500	1.544	1.549	OOOX
XXXX	0.555	0.896	0.985	1.007	OOOO
	X	XX	XXX	XXXX	Second part of serial
	-K : Tests serial				

X = dead animal. **O = survival Animal.**