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Public Health and Unrealistic Regulatory Policy on drug Discovery and Development: Insight review.

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Background:

Research and drug development industries have debatable, multiphase drug screening procedures in which harmful products could still be infiltrated and reached the Pharmaceutical market as health service delivery to the public. This happens because the door is open for harmful products to be on the market in a way that follows:

Main body:

A wide range of test chemical substances have delayed manifestation of undesired effect on the study subject with the time to undesired effect after acute exposure being weeks and months. Acute toxicology in a preclinical trial, for instance, has limited clinical value due to the fact that its lethal dose is the endpoint for a conclusion in which death sometimes occurs after a scheduled period of acute toxicology. Countless resources are being wasted and a number of new drugs are introduced into the pharmaceutical market with assumption safety analysis every year due to unscientific grounds in preclinical trials. The principal use of collected data from a preclinical trial is to support regulatory categorization and harmful labelling decisions that the data can also be used to derive safe use threshold levels which may lead to use of unsafe material. The criteria for classification and labelling also differs among countries, sometimes among authorities within the same country. The principle of toxicology, on the other hand, is vaguely stated that 'all chemical substances are potential poisons depending on the amount and duration of exposure' in which the nature of any chemical substance could not be changed by simply quantification. The toxic nature of a test chemical could neither be created nor eliminated by simply limiting the amount that has to be administered to study animals.

Conclusion:

All xenobiotics are poisons at any amount with different intensity that could be measured using biological parameters.

Keywords: Drug Policy, Public Health, preclinical trials, Toxicology, Research,

1.0: Backgrounds

A preclinical trial is a basic step in the development of unknown drugs into pharmacological products in which multiple assumption procedures are still involved in the practice. The first step of a preclinical trial is to determine the safety margin after administration of a single dose of test drug in one of drug administration routes during the period of the experiment which might not be exceeding 24 hrs [1-3]. It is usually conducted to support the development of new drugs or medicine where the death of study subject is an endpoint for a conclusion [2-3]. The use of lethal effect as an endpoint for a conclusion, however, makes acute toxicity study less valuable in safety regulatory measures [2-3]. There is no specific minimum lethal dose and maximum non-lethal dose for every test

chemical substance that could be manifested within 24 hours [1]. The different levels of doses has a different length of time at which it could cause a significant pharmacological effect in treated subjects [1-3]. The range of doses that can cause a lethal effect to treated study animals also varies extensively because of strain, age and sex of the study animal and route of drug administration [4]. According to the current existing guidelines, however, the objective of acute toxicity study is to identify the dose which causes major adverse effects and an estimation of a minimum lethal dose within 24 hours which has no adequate scientific grounds [5]. It has limited value in terms of preclinical and human safety assessment because of the adverse effect of considerable test chemicals manifested after 24 and 48 hours being administered to a study subject [2]. There is no clinical pathology, immunology or other clinical measures conducted in acute toxicity studies to validate the data with adequate scientific background [2-3]. Generally, Preclinical study has still controversy on both ethical and scientific grounds in which more time and resources are unnecessarily used in assessment of lethal endpoint study with limited scientific toxicity analyses.

Death usually happens as a result of loss of bodyweight (wasting syndrome) from test chemical induced inhibition of gluconeogenesis and appetite suppression [5]. Therefore, a test chemical substance said to be toxic not only when it causes death but also a pharmacological mechanism against the biology of treated organism which may not cause death within the scheduled period of preclinical trials [2-3]. The administered test chemical substance may manifest its undesired effect at the cellular or organismal level depending on the amount of dose which may cause death at different lengths of time after dosing [1]. The amount of a dose therefore determines the magnitude of undesired biological response which determines the lifespan of exposed study animals [2-3]. Death usually happens when the impaired part of the biological organ or system outweighs the viable part in the diseased organism [2-3]. Death is, therefore, used to denote an organism that has lost bio-physiological interaction with its environment where it has existed for years and decades [2-3]. The different levels of doses prepared from a test chemical substance may manifest its toxic effect on treated study animal with different magnitude at different lengths of time depending on the amount of dose administered into the biological system. If the higher dose is lethal to the study subject, then the lower dose is most likely to have undesired effects in the long run [2-3]. The previous studies conducted by Belay in 2011 and 2019 showed that there is no scientific ground to categorise the different levels of doses of a test chemical as a safe dose (ED_{50}) and lethal dose (LD_{50}) to the treated laboratory animals within the period of the experiment [1-3]. The lower dose could not be safe for health when the higher dose is lethal [1-3]. It is most likely to be a waste of time and resources to categorise a single test substance as an effective dose (ED_{50}) and lethal dose (LD_{50}) and proceed to the next phase of preclinical trials with inadequately validated data [1]. Countless resources are being wasted every year and harmful pharmaceutical products are infiltrating to the public for consumption due to unrealistic regulatory procedures in preclinical trials by which the lethal dose is the endpoint for a conclusion [1]. A dose which is highly toxic to one species could not have the same pharmacological effect on another species [2-3]. A dose of a test chemical substance may not even have the same pharmacological effect on the same species of animal due to differences in the strength of immune responses,and biological sensitivity [6].

There are considerable discoveries of therapeutic agent every year but the speed at which those discoveries lead to improved health has been frustratingly lagging [7]. When we succeeded in controlling infectious diseases, we failed to control non-communicable diseases such as cancer because of lack of realistic drug regulatory policy in drug discovery and development and malpractice in healthcare service. Local communities in the third world, for instance, have still used traditional medicines as means of preventing and treating new and re-emerging diseases with unrealistic clinical analysis which might contribute to the current high incidence of cancer across the world [1]. The study conducted by Belay in 2011 showed that ethanol and ether test extracts from the dried seed of traditional medicinal plant, known as Aristolochia elegans mast, caused severe damage to the kidney and liver of treated Balb c mice [1]. Four out of 10 treated Balb c mice were also developed hemorrhages in the stomach which were strong evidence of carcinogenic property of this plant material [1]. Different local community members has been using this herbal product with different dosage forms against malaria

parasites [1]. The study concluded that a person using this herbal preparation is at a higher risk of getting stomach cancer and renal and hepatic diseases.

The strategy for preclinical trials has been changed significantly over the last many years in order to ensure that early toxicological data can help to make decisions on the best compounds to progress as valuable human medicines [8, 9]. There is still, however, an urgent need to create a research setting with realistic research guidelines that have a holistic biological approach in order to be able to accelerate the development of safe therapeutic agents with minimum expenditure within the shortest possible time. The rate of unsuccessful clinical trial in the development of a safe therapeutic agent is still frustrating in which an enormous amount of money is being spent in drug discovery and development that doesn't work. We need to have a validated research system with a holistic biological approach that could better predict the potential therapeutic agent at the earliest possible stage of preclinical trials. Clinical and immunological evaluation needs to be conducted regularly for adequate time during a preclinical trial for the adequacy of public health safety.

2.0: Construction and content

Preclinical data on dose-biological response relationship of different test chemicals has been selected based on clinical and immunological parameters from the two studies which was published by Belay in 2011 and 2019. The selected data has been analysed manually and using Microsoft word 2013 and smartphone with a calculator for further technical and biological contents that might provide realistic research guidelines in preclinical trials. The subject matter of each data has been identified and organized into meaningful categories and sub–categories which is described in the next section with respective headings. The preclinical data from different data sources has been compiled to define research guidelines in drug discovery and development.

3.0: Utility and discussion

The previous studies conducted in 2011 and 2019 have revealed that the dose has no role to avoid the toxicity of a test chemical but it has the role to limit the magnitude of pharmacological effect which determines the length of time at which gross biological response could be manifested on treated study animals [10]. The higher the dose of a test chemical, the shorter the length of time at which sign of undesired biological effect could be manifested on exposed study animals. The toxic property of a chemical substance is also being diverse in which an integrated biological approach has to be considered to analyse its toxicity in a harmonized manner to limit unnecessary wastage of time and resources [10]. The selected and analysed preclinical data from different biological perspectives has been, therefore, used in this article to outline and discuss the crucial steps in preclinical trials which is described as follows:

3.1: Steps in a preclinical trial of a test chemical

3.1.1: Identity and chemical structure, physical and chemical properties

Doing the right thing at the right time is an essential principle to easily achieve a desired goal. There are essential steps in preclinical trials to be followed to avoid unnecessary wastage of time and resources. The toxic property of most chemical substances is created from the component of its chemical structure during metabolism in which it could not be eliminated by limiting the amount that has to be administered to a study subject. It is, therefore, necessary to have an information about the identity and chemical structure, physical and chemical properties and the result of any other toxicity tests before a preclinical trial of a test chemical [9]. This information is important to make a preliminary decision whether or not a test chemical is relevant for the development of a safe therapeutic agent. This preliminary information could also be helpful in the selection of an appropriate level of doses for the experiment. As a rule, the different levels of doses need to be determined including the lowest and the highest possible dose shortly before testing.

3.1.2: Recruitment and sampling of study animals

The second activity in drug trial has to be recruitment of preferred study animals for a preclinical trial and kept them in the laboratory animal-friendly environment where there is normal sequence of dark and light cycles. The previous studies in 2011 and 2019 showed that there is no need to sample more than two mice

for each dose as well as multiphase drug screening procedures in preclinical trails which leads to unnecessary wastage of time and resources. All preclinical phases could be evaluated in a single drug screening procedure. The previous studies conducted in 2011 and 2019 also showed that there is no need of sampling different species or sex of lab animals for the experiment because the toxicity of any test chemical could even vary within the same species of animals depending on the strength of the immune response [2-3]. After grouping in cages based on experimental protocols and acclimatising in the new environment for a minimum of five days, the biological condition specifically the immune strength of each sampled animals need to be evaluated 3 days before the administration of prepared doses for a comparison after dosing as shown in Table 1.

3.1.3: Testing procedure

The third activity in a preclinical trial of a test chemical is the preparation of different levels of doses that has been selected shortly before being administered to study animals using preferred route of drug administration. The time at which a test chemical administered to the biological system of study animal need to be recorded in notebook as shown in Table 2. The treated study animals should be monitored for any sign of toxicity while feeding them with conventional laboratory diets with unrestricted supply of drinking water throughout the experiment [9]. An observational investigation should be carried out at least for two hours three times a day (immediately after dosing, 4 and 10 hours after dosing). The time at which sign of toxicity manifested on treated study animal i.e. slow activity, suppressed appetite, tearing, salvation, and so on need to be recorded in notebook as shown in Table 3. The strength of immune response against tested chemicals and body weight of treated study animals need to be evaluated at least once every five days with having the first evaluation at four hours after dosing during the period of a preclinical trial as shown in Table 1 [2]. The collected data should be processed and expressed in quantitative biological responses as toxic severity and toxic reaction rate of each administered doses to a study animal to be able to determine the clinical fate of tested chemical. Quantitative biological responses as toxic severity and toxic reaction rate of an administered dose of a test chemical was determined using the following mathematical formulas during the previous two studies conducted in 2011 and 2019 which is explained in details in section 3.1.5:

Formula 1 → s=(r/d x 100)%/sec and formula 2→ r=(d/t-ΔIg) mg/sec, where s is toxic severity, r is toxic reaction rate, d is the administered dose, t is the length of time at which sign of toxicity manifested on treated study animals, and ΔIg is the changes in the concentration of serum immunoglobulin after dosing. Three test chemicals at different levels of doses (10, 50, and 90) mg/kg were administered to nine laboratory animals (one mouse for each dose) in the oral route and monitored for possible signs of toxicity for five days. The preclinical data has been extracted from exposed study animals and recorded in note book as shown in Table 1. 2. 4 and 5.

Table 1:

Changes in serum immunoglobulins concentration (Δ Ig) after treatment of study animals with different levels of doses of test chemicals (Belay 2019).

Test drugs	Tested doses	Quantitative immunoassay before treatment as reference test		Quantitative immunoassay four hours after treatment for comparison		Δ Ig serum conc.
		IgG	IgM	IgG	IgM	Δ *Ig*
Dichlorvos	10 mg/kg	<1100 mg/L	70 mg/L	<1100 mg/L	90 mg/L	+20 mg/L
	50 mg/kg	<1100 mg/L	70 mg/L	<1100 mg/L	80 mg/L	+10 mg/L
	90mg/kg	X	X	X	X	X
Chlorpyrifos	10 mg/kg	<1100 mg/L	90 mg/L	<1100 mg/L	120 mg/L	+30 mg/L
	50 mg/kg	<1100 mg/L	50 mg/L	<1100 mg/L	70 mg/L	+20 mg/L
	90mg/kg	<1100 mg/L	90 mg/L	<1100 mg/L	80 mg/L	-10 mg/L
Cypermethrin	10mg/kg	<1100 mg/L	70 mg/L	<1100 mg/L	90 mg/L	+20 mg/L
	50 mg/kg	<1100 mg/L	80 mg/L	<1100 mg/L	70 mg/L	-10 mg/L
	90 mg/kg	<1100 mg/L	80 mg/L	<1100 mg/L	50 mg/L	-30 mg/L

X in table 1, 4 & 5 represents sampled study animals which died earlier than the time for data collection.

Table 2:

The length of time at which adverse biological effect significantly manifested on study animals treated with test chemicals orally [Belay 2019].

Test Drugs	Doses tested	№ of Mice	Weight in *gm*	Time at which test substance administered	Time at which signs of adverse effect clearly manifested	Duration
Dichlorvos	10 mg/kg	1	15.13	10:22	11:22	1 hour
	50 mg/kg	1	17.63	10:23	10:53	30 minutes
	90 mg/kg	1	16.42	10:24	10:39	15 minutes
Chlorpyrifos	10 mg/kg	1	30.41	10:28	13:00	2:30 hours
	50 mg/kg	1	27.12	10:29	12:00	1:30 hours
	90 mg/kg	1	26.84	10:30	11:00	30 minutes
Cypermethrin	10 mg/kg	1	28.42	10:32	10:55	23 minutes
	50 mg/kg	1	30.98	10:33	10:45	12 minutes
	90 mg/kg	1	28.24	10:36	10:45	9 minutes

Table 3:

The length of time at which test extracts caused lethal effect to Balb c mice at different levels of doses [Belay 2011].

Dose in mg/kg	500 & 1000	2000 & 3000	4000 & 5000	Distilled H_2O (0.5ml)	Cooking oil (0.5ml)
Number of treated mice	8 	8 	8 	4 	2 
Adverse effect within 24 hrs	Nil	Nil	Nil	Nil	Nil
Within 48 hrs	Nil	Nil	Nil	Nil	Nil
Within 72 hrs	Nil	Nil	Depressed appetite	Nil	Nil
Within 96 hrs	Nil	Depressed appetite	2 mice died	Nil	Nil
Within 120 hrs	Nil	1 mouse died	2 mice died	Nil	Nil
Within 144 hrs	Depressed appetite	3 mice died	4 mice died	Nil	Nil
Within 168 hrs	2 mice died	4 Mice died		Nil	Nil
Within 192 hrs	2 mice died			Nil	Nil
Within 216 hrs	4 mice died			Nil	Nil

Table 4:

Toxic severity (s) of test chemicals computed at 4 hours after dosing (Belay 2019).

Test drugs	Doses tested	Toxic severity (s) in %/sec
Dichlorvos	10 mg/kg	-199.0
	50 mg/kg	-19.8
	90 mg/kg	X
Chlorpyrifos	10 mg/kg	-299.0
	50 mg/kg	-39.8
	90 mg/kg	11.1
Cypermethrin	10 mg/kg	-199.0
	50 mg/kg	20.0
	90 mg/kg	33.3

Table 5:

Toxic reaction rate (r) of test chemicals computed at four hours after dosing.

Test drugs	Doses tested	Approximate length of time undesired effect significantly manifested	Toxic reaction rate (r) in ^{mg}/sec
Dichlorvos	10 mg/kg	60 minutes	-19.9
	50 mg/kg	30 minutes	-9.9
	90 mg/kg	15 minutes	X
Chlorpyrifos	10 mg/kg	2:30 hours	-29.9
	50 mg/kg	1:30 hours	-19.9
	90 mg/kg	30 minutes	10.0
Cypermethrin	10 mg/kg	25 minutes	-19.9
	50 mg/kg	12 minutes	10.0
	90 mg/kg	9 minute	30.0

3.1.4: Immunoassay after dosing

The immune system is usually activated by biological molecules known as immunoglobulins to protect the body from harmful antigens. The immunoglobulins provide services to the body as cell surface receptors for antigen which allows cell signaling and cell activation [11]. It also serves as an effector molecules that can bind and neutralize antigens invaded the biological system [11]. Immunoassay usually conducted to assess the normality and functionality of the immune system because it is the ultimate indicator of the wellbeing of an organism. As we could hardly expect rain from the sky's horizon without clouds, it is equally hard to expect the wellbeing of a human with having abnormal immunoglobulins concentration in blood serum. The abnormality in immune response may refer to an elevated or suppressed immunoglobulins concentration in blood serum [12-14]. When noxious chemicals incorporated into the biological system and cause abnormal biological mechanisms, the adverse effect could be manifested either by elevating or suppressing the immune response depending on the chemical nature of a drug. A chemical substance that elevates the immune response of treated study animal, is most likely to be an inflammatory drug which causes an inflammatory disease [15, 16]. Inflammation refers to a painful reaction resulted from the interaction between a noxious chemical and a biological component which perhaps damage or destroy a biological system. Pain, on the other hand, is a complex physiological phenomenon with a feeling of physical suffering resulted from the adverse chemical reaction against the integrity of biological tissue. This kind of drug is mainly cytotoxic and has a high risk of causing adverse drug reaction within the biological system of an organism [17]. The lower doses

prepared from the three test chemicals mentioned in table 1 disproportionately increased the immune response during the first 4 hours after dosing while the higher dose disproportionately suppressed the immune response of treated Balb c mice which is demonstrated as drug B in figure 1. This shows that as the inflammatory action of a drug increases, it disrupts the normal physiological mechanism that would affect the metabolic system of an exposed organism which ultimately deteriorates the immune response as the two systems directly dependent on one another [16]. This category of drugs usually manifests gross biological responses very shortly after dosing (Table 1).

The second category of chemical substances are those drugs that directly suppress the immune response which is also directly harmful to the metabolic system of an organism. It is mainly characterized by depressed appetite and slow activity of treated study animals as it is demonstrated in table 3 [1]. This category of drugs is mainly subcategorized as mutagens and carcinogens most of which are genotoxic that takes a very long time to manifest its gross biological effect after dosing [18]. It disrupts the normal function of the genome which architects the bio-physiological network of the body which again disrupts the normal physiological activity that leads into an abnormal function of the metabolic system which ultimately deteriorates the strength of the immune response by gradually slowing down to the lowest level as shown in figure 1, drug A. They usually manifest silent undesired biological mechanism which might become a hereditary or nonhereditary disease [19]. If it has damaged the germ cell and caused hereditary disorder, it could spread in the population through reproduction in which its incidence increases as the population increases [20]. Today, there are thousands and millions of anomalies related to genetic disorders with an unknown cause.

The administered test chemical could affect the metabolic system in different ways which ultimately manifested in the immune response. It might be directly toxic to the cellular metabolism or neurotoxic that disrupts the normal physiological activity of the body which ultimately impacts the metabolic and immune system of an organism. In a general description, whenever there is abnormal bio-physiological mechanism manifested within the biological systems, the undesired effect would be manifested by elevating or suppressing the immune response (Figure 1). The immune response is a complex biological mechanism which acts to protect the biological system of an organism exposed to etiologic agents such as noxious chemicals mentioned earlier. The three test chemicals mentioned above significantly suppressed the immune response as the level of doses administered into study animals increased from 10 to 90 mg/kg body weight (Table 1). This simply implies that the test chemicals are not biological friendly to be considered in the development of pharmaceutical or nutraceutical products out of it. However, the immunoassay should be conducted for adequate length of time to adequately validate the data for a conclusion. Since drawing blood samples for immunoassay on daily basis could affect the biological condition of study animals, it is preferable to do it at least once every five days during the period of a preclinical trial.

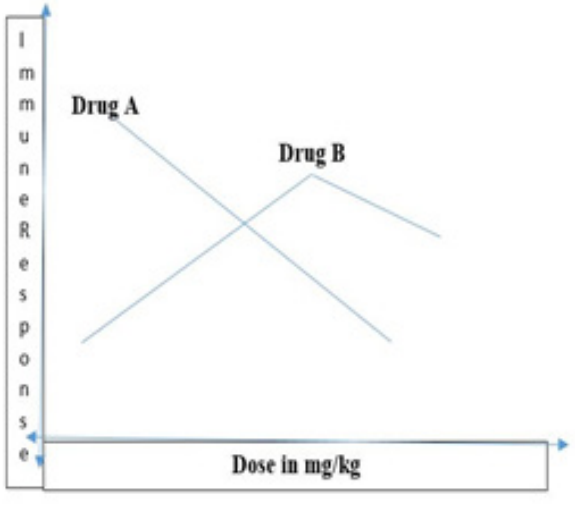

Figure 1:

Diagram showing the immune response against drug A and drug B

3.1.5: Data interpreting

Data interpreting in a preclinical trial usually leads to failure when it has interpreted without having the detailed information about the dose-biological response relationship with adequate time of investigation. It is important to note that a dose could not change the pharmacological property of a test chemical substances administered to study animals. The amount of a dose, however, changes the magnitude of the

pharmacological effect of a test chemical that could determine the length of time at which gross biological responses may manifest on the treated study animals [10]. The different levels of doses prepared from the same test chemical mentioned in table 2 and 3 that have been administered to study animals were manifested undesired biological responses at different length of time after dosing orally. The dose had no role to avoid toxicity but rather determined the magnitude of biological response that could determine the lifespan of exposed animals [2-3]. The gross biological responses against each administered doses need to be computed as the toxic severity and toxic reaction rate to determine the fate of a test chemical as expressed in Table 4 and 5 respectively.

3.1.5. A: The toxic severity of a dose

The toxic severity is the magnitude of undesired biological response caused by the administered dose of a test chemical which is expressed in percent per second (%/sec). It represents the approximate proportion of biological harm that has been manifested as gross biological response on exposed animal. It could be expressed quantitatively using an integrated biological approach with the mathematical formulation mentioned in formula 1 earlier. The toxic severity of the three test chemicals administered to lab Balb c mice at a dose of 10 mg/kg shown in table 4 was computed at four hours after dosing as follows:

1. The toxic severity of a dose at 10 mg/kg prepared from Dichlorvos pesticide:

s=(r/d x100)%/sec
s=((-19.9 mg/sec)/(10 mg/kg) x100)%/sec
s=-199.0 %/sec

2. The toxic severity of a dose at 10 mg/kg prepared from Chlorpyrifos pesticide:

s=(r/d x100)%/sec
s=((-29.9 mg/sec)/(10 mg/kg) x100)%/sec,
s=-299.o %/sec

3. The toxic severity of a dose at 10 mg/kg prepared from Cypermethrin pesticide:

s=(r/d x100)%/sec
s=((-19.9 mg/sec)/(10 mg/kg) x100)%/sec
s=-199.0 %/sec

The toxic severity of a dose prepared from the three test chemicals and administered to study animals at 10 mg/kg body weight was less than zero as shown in the calculations above. This implies to the reason that the three tested chemicals at a dose of 10 mg/kg caused adverse biological response which is negligible at the organismal level due to the fact that it has boosted the immune response which neutralizes the toxic severity (Table 1). This, however, does not prove that tested chemicals are safe at the cellular level [2-3]. An increase in the immune response might be due to inflammatory or irritating action of administered test chemicals that could not be safe at the cellular level. The intensity of toxic severity was not significantly manifested at the organismal level during the first four hours after being administered to Balb c mice orally because of an increase in the immune response. A significant adverse biological effect of lower doses might be manifested in the long run within the lifespan of exposed study animals. Multiple immunoassay, therefore, needs to be conducted at least for 15 days (once every five days) after dosing to better validate that a test chemical at 10 mg/kg is safe at the cellular level. The toxic severity of a dose at 90 mg/kg prepared from the three test chemicals, however, was significantly manifested gross biological response during the first four hours after dosing orally which was computed as follows:

1. The toxic severity of a dose at 90 mg/kg prepared from Chlorpyrifos pesticide:

s=(r/d x100)%/sec
s=((10 mg/sec)/(90 mg/kg) x100)%/sec
s= 11.1 %/sec

2. The toxic severity of a dose at 90 mg/kg prepared from Cypermethrin pesticide:

s=(r/d x100)%/sec
s=((30 mg/sec)/(90 mg/kg) x100)%/sec
s= 33.3%/sec

This means that the administered dose at 90 mg/kg, which is prepared from Chlorpyrifos and Cypermethrin pesticide, has been caused 1110 times and 3330 times biological injury or harm in every second respectively. This again implies that the administered dose at 90 mg/kg prepared from each test chemicals could manifest gross biological responses on treated laboratory animal with a body mass of approximately 12.3 kg [s/d=(1110/sec)/(90 mg/kg)=12.3 kg)] and 37 kg [s/d=(3330/sec)/(90 mg/kg)=37 kg)] depending on the strength of the immune response respectively.

The computed toxic severity of a dose administered to study subject could, therefore, help to determine the possible maximum effective dose to the body weight of treated study animal to be used in the development of pharmaceutical products. The maximum dose of a test chemical that has computed toxic severity and toxic reaction rate less than zero could be considered in the development of therapeutic agent if it is proved to be non-genotoxic or non-cytotoxic. The toxic severity and toxic reaction rate of a dose need to be evaluated for adequate period of time (once every five days) to adequately validate the data that a test chemical is safe for health.

3.1.5. B: The toxic reaction rate of a dose

The toxic reaction rate is the amount of administered test drug that has elicited adverse biological effect on exposed study animals that has been detected at the organismal level. It represents the approximate amount of administered test chemical that has been reached the vicinity of drug receptor or biological target and cause gross adverse biological response which is expressed in milligram per second (mg/sec). It could also be expressed quantitatively using an integrated biological approach with the mathematical formulation mentioned in formula 2 earlier. The administered doses prepared from Dichlorvos and Chlorpyrifos at 10 and 50 mg/kg caused a toxic reaction rate which was less than zero (Table 5). The toxic reaction rate of Dichlorvos and Chlorpyrifos administered to lab Balb c mice at a dose of 10 and 50 mg/kg shown in table 5 was computed as follows:

1. The toxic reaction rate of a dose at 10 and 50 mg/kg prepared from Dichlorvos test chemical.

a. r=(d/t-ΔIg) mg/sec
r=((10 mg/sec)/(14,400 sec)-20 mg/L)mg/sec
= -19.9 mg/sec

b. r=(d/t-ΔIg)mg/sec
r=((50 mg/sec)/(14,400 sec)-10 mg/L)mg/sec
= -9.9 mg/sec

2. The toxic reaction rate of a dose at 10 and 50 mg/kg prepared from Chlorpyrifos test chemical.

a. r=(d/t-ΔIg)mg/sec
r=((10 mg/sec)/(14,400 sec)-30 mg/L)mg/kg,
r = -29.9 mg/sec

b. r=(d/t-ΔIg)mg/sec
r=((50 mg/sec)/(14,400 sec)-20 mg/sec) mg/sec,
r = -19.9 mg/sec.

The toxic reaction rate of a dose at 10 and 50mg/kg prepared from each test chemicals was less than zero as shown in the calculations above. This means that negligible amount of drug has reached the vicinity of the drug receptor or biological target due to the fact that each doses has boosted the immune response which antagonizes/neutralizes the toxic reaction rate of tested dose (Table 3 and 1). Further investigation needs to be done for adequate length of time at which the toxic reaction rate should also be calculated to adequately validate the data. The administered test chemicals at a dose of 90 mg/kg which was prepared from Chlorpyrifos and Cypermethrin, however, caused a toxic reaction rate of 10 mg/sec and 30 mg/sec respectively (Table 5). This implies that, of the administered doses at 90 mg/kg from both test chemicals, 11.1% and 33.3% have reached the vicinity of drug receptor or biological target that has been elicited gross biological responses on treated Balb c mice. This again implies that Cypermethrin is more toxic than Chlorpyrifos.

4.0: Conclusions

The toxic property of a test chemical is diverse, has a variety of adverse effects which makes preclinical trials very challenging to monitor and evaluate the outcome of the experiment. A chemical substance that is safe to the liver, might be toxic to the kidney. A chemical substance that is safe to the respiratory system, might be harmful to the digestive system. Whatever tissue, organ or organ systems are affected by the administered test chemicals, the adverse effect is, however, directly manifested on the immune system of treated study animals. It is, therefore, required a holistic biological approach to be able to analyse it in a harmonized manner. The holistic biological approach has to take consideration of the administered dose, the length of time at which signs and symptoms of toxicity manifested on treated animals, and changes in the concentration of immunoglobulins in blood serum.

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