Physiological and Biochemical Evaluation of Fomesafen Toxicity in Female Albino Wistar Rats

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A B S T R A C T

Fomesafen is widely used as herbicide for weed control. Fomesafen have both foliar and soil activity. It mostly control broadleaves. Fomesafen is labeled for postemergence applications to soybeans, peanuts, and rice. Although bronzing or burning of soybean leaf tissue is evident after application, yield is rarely affected. The present study was designed to evaluate the effect of repeated exposure of Fomesafen (Herbicide) by oral gavage method on the blood biochemistry of female wistar rats. The study highlights the various changes in biochemical parameters of female wistar rats over repeated exposure by Fomesafen by oral route through gavage. Under the conditions of this study, the repeated oral administration of 'Fomesafen technical' in Female wistar rats at the dosage level of 50 mg/kg b.wt. for consecutive 90 days did not induce any observable toxic effects, alteration in blood biochemistry parameters when compared to its corresponding control group of animals.

Introduction

The use of herbicides is increasing in worldwide crop production. The value of the worldwide herbicide market grew by 39% between 2002 and 2011 and is projected to grow by another 11% by 2016 (Philips McDougall, 2013). Herbicides are being rapidly adopted in developing countries that face shortages of hand weeding labor and the need to raise crop yields (Zhang, 2003). Improved weed control with herbicides has the potential greatly to improve crop yields in many developing countries in the near future (Masthan *et al.,* 1989). Increased herbicide use promotes fertilizer use, which leads to even greater yield increases (Manda, 2011).

Research has shown that, if enough hand weeding is done at the optimal times, crop yields are not reduced by weed competition (Prasad *et al.,* 2008). In reality, crop fields are seldom adequately weeded by hand; weeding is tedious and time consuming. Laborers are not always available when needed (De Datta and Barker, 1997). Weeding is often done late, causing drastic losses in yield (Rashid *et al.,* 2012). The use of herbicides has gained impetus from the general rise in farm wages as a consequence of overall economic growth and growth in non-farm employment opportunities, particularly in Asia adequate non-chemical controls for weeds are not

available, and herbicide use is increasing dramatically as a result of rising opportunity costs of labor across the developing world (Pingali and Gerpacio, 1997). Herbicide use is increasing in many countries where tillage and flooding for weed control are being reduced in order to conserve natural resources: soil, water and energy.

Selective herbicides kill certain targets while leaving the desired crop relatively unharmed. Some of these act by interfering with the growth of the weed and are often based on plant hormones. Herbicides used to clear waste ground are nonselective and kill all plant material with which they come into contact. Some plants produce natural herbicides, such as the genus Juglans (walnuts). Herbicides are widely used in agriculture and in landscape turf management. They are applied in total vegetation control (TVC) programs for maintenance of highways and railroads. Smaller quantities are used in forestry, pasture systems, and management of areas set aside as wildlife habitat. Herbicides have been alleged to cause a variety of health effects ranging from skin rashes to death. The pathway of attack can arise from improper application resulting in direct contact with field workers, inhalation of aerial sprays, food consumption and from contact with residual soil contamination. Herbicides can also be transported via surface runoff to contaminate distant surface waters and hence another pathway of ingestion through extraction of those surface waters for drinking. Some herbicides decompose rapidly in soils and other types have more persistent characteristics with longer environmental half-lives. In Asia, particularly in the Philippines; the proportion of rice farmers using herbicides increased from 14% in 1966 to 61% in 1974 (De Datta and Barker, 1997). Today, 96–98% of Philippine rice farmers use herbicides (Marsh, 2009). A recent study determined that, with increased labor cost, herbicide application in rice fields is superior to manual weeding even at the lowest weed density by \$US 25–54 ha. At the highest weed density and highest labor cost, herbicide application is approximately 80% (about \$US 200 per ha) more profitable than hand weeding (Beltran *et al.,* 2012). In Bangladesh, the loss in rice yield in farmers' fields as a result of poor weeds control has been determined to be 43–51% (Rashid *et al.,* 2012). The yield gap between herbicide use and hand weeding is as high as 1 metric t ha^{-1}, with 30% of farmers losing in excess of 500 kg ha^{-1} in the absence of herbicides

Trends of herbicide consumption in the world and its expenditure Annual usage of herbicides in the world was about 4000 million pounds in the 1953's, increasing to nearly 121000 million pounds at the end of 2013 (WAP, 2014). Since then, at the end of each five years 15-24% increment occurred (Fig. 3). The herbicide industry is quite significant in dollar terms. Annual expenditures by users of herbicide totaled about \$US33 billion in 1953 and \$US 998 at the end of 2013 (Fig. 4). It is clear from the figure that, there is a sharp increasing trend in consuming herbicides which triggers to increase the market expenditure for herbicides. In future, by the end of 2025, it is supposed the herbicides consumption to be increased by 150 000 million pounds which will costs around \$US 2000. The present study was designed by dividing the 60 female wistar rats into six groups (G1 – G6), blood collection was done under light anesthesia (CO_2) through retro orbital sinuses and different biochemical parameter like Glucose (mg/dl), Serum Glutamate Oxaloacetate Transferase (U/L), Serum Glutamate Pyruvate Transferase (U/L), Blood Urea Nitrogen (mg/dl), Serum Alkaline Phosphatase (U/L), Total Protein (g/dl), Sodium (mEq/L), Potassium (mEq/L), Cholride (mEq/L) and Cholinesterase (U/L) were studied using Beckman Coulter AU480 Clinical Chemistry autoanalyser system.

Methods and Materials

Animal selection

The Female Wistar Rat of age 5-8 weeks and body weight in the range 100-140 gm of was selected for use in this study due to availability of comprehensive background data relating to pathological and clinical parameters, at this laboratory; widely used as a species to predict toxicity of the test item in human and larger animals.

Animal identification and acclimatization

Animal identification was done with the help of marking ink. Each cage was tagged with appropriate label mentioning the description of study number, study name, dose level, group name, animal number, sex of the animal, date of initiation of experiment, date of dosing and date of completion of the experiment. Acclimatization of the animal was done before initiation of dosing during experiment period the animals were housed in animal house and the husbandry done under good environmental Conditions.

Environmental conditions and maintenance of animals

The experimental room was monitored for temperature, humidity, light intensity and air changes. The room temperature was maintained at 22±3°C with 50-60 % relative humidity. The room was ventilated at the rate of approximately 15 air changes per hour and lighting was controlled to give 12 hours artificial light (8 a.m-8 p.m) each day. Whereas; housing of animals is done randomly selected animals were caged in a group of 5 according to sex in polypropylene rat cages fitted with wire mesh tops and having autoclaved clean corn Cobb bedding. A sample of bedding material was analyzed for microbiological and chemical contaminants on a routine basis (Chauhan *et al.,* 2015). There were no known contaminants in the bedding material. Animals were feed with Sterilized standard pellet feed (Amrut Feeds Ltd.) and available *ad libitum* to the experimental animals. The quality of feed was regularly monitored at the NABL accredited laboratory of Shriram Institute for Industrial Research. There were no known contaminants in the feed at levels that would have potential to influence the outcome of this study. Drinking Filtered drinking water was available *ad libitum* to the experimental animals through polypropylene bottles fitted with nozzles. The quality of water was regularly monitored at the NABL accredited laboratory of Shriram Institute for Industrial Research. There were no known contaminants in the water at levels that would have potential to influence the outcome of this study.

Animal welfare

All animals were handled with similar due regard for their welfare and the conditions in accordance to the standard operating procedures in compliance with the regulations of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India. Room sanitation was done **o**n routine basis, the floor, work tops of the experimental room was swept and mopped with a disinfectant solution (D - 125/D-256).

Acute oral toxicity study

In the assessment and evaluation the toxic characteristic of a test item, determination of 'Acute oral toxicity in wistar rats' is usually a stepwise procedure. This study was hence, performed to assess the acute oral toxicity of 'Fomesafen Technical' in wistar rat, A study at the dose of 2000 mg/kg B.wt. was conducted, taking 3 females rats (nulliparous and non pregnant) as per the recommendation of the guideline (OECD No.423). A single

oral gavage dose was administered to the animals with the help of cannula attached to a syringe. The animals were fasted overnight prior to dosing.

Repeated oral exposure study

A total of 60 females were selected and randomly distributed into six groups with 10 animals /group. At the commencement of the study, the weight variation of animals used, was minimal and did not exceed ± 20 % of the mean weight of each group. Four groups of 10 female rats were administered with test item 'Fomesafen technical' at the dose levels of 0, 50, 100 and 250 mg/kg B.wt and two additional recovery groups of 10 female each at the dose level of 0, 100 mg/kg B.wt. were administered with test item 'Fomesafen technical' by oral route over a period for 90 days. The blood collection of rats was done by deeply anesthetized by exposure to CO_2. The depth of anesthesia was assured by the constriction of the pupils as well as simple sensory tests, such as the absence of eye blinking when the eyelid was touched and the absence of foot withdrawal when the foot was pinched. Blood was collected by orbital sinuses for interim evaluation of blood biochemistry parameter and for terminal sacrifice the thoracic cavity was opened. Whole blood was collected in EDTA vacutainer tubes via abdominal aorta The biochemical parameters e.g. Glucose (mg/dl), Serum Glutamate Oxaloacetate Transferase (U/L), Serum Glutamate Pyruvate Transferase (U/L), Blood Urea Nitrogen (mg/dl), Serum Alkaline Phosphatase (U/L), Total Protein (g/dl), Sodium (mEq/L), Potassium (mEq/L), Cholride (mEq/L) and Cholinesterase (U/L) were studied using Beckman Coulter AU480 Clinical Chemistry autoanalyser system.

Dose preparation

Different doses were prepared in corn oil in calibrated volumetric flasks at the dose levels of 50 mg/kg b.wt, 100 mg/kg b.wt. and 250 mg/kg b.wt. for low, intermediate and high dose groups respectively and 100 mg/kg b.wt. for recovery intermediate dose group. Doses were prepared freshly prior to dosing. Administration of dose was done 10 ml/kg body weight was maintained for each rat. All rats were dosed by gavage using a cannula attached to a syringe.

Statistical analysis

All the Statistical analysis were done using MiniTab 16.0. Standard errors and one way ANOVA were calculated for given data

Results and Discussion

The Acute study was performed before the initiation of main study i.e. repeated exposure study with Fomesafen on female wistar rats. In Acute study the expose animal via oral route showed No treatment related toxic signs and symptoms or mortality in any of the animal at the dose level of 2000 mg/kg B.wt. Under the conditions of this study, no toxic sign and symptoms/mortality was observed in any of the animals at the maximum dose level of 2000 mg/kg B.wt. Hence, the LD50 range of 'Fomesafen Technical' lies between >2000-5000 mg/kg B.wt. and is categorized as 2000 mg/kg < LD50 < 5000 mg/kg (Category 5) as per the Globally Harmonized Classification System (GHS). Based on the observation of acute study a main study was designed with 60 females wistar rats and grouped into six group (G1 – G6) Four groups of 10 female rats were administered with test item 'Fomesafen technical' at the dose levels of 0, 50, 100 and 250 mg/kg B.wt and two additional recovery groups of 10 female each at the dose level of 0, 100 mg/kg B.wt. were administered with test item 'Fomesafen technical' by oral route over a period for 90 days.

Table.1 Experimental design

Group	Dosage Level (mg/kg B.wt.)	Animals used	Terminal Sacrifice (Sacrificed after 90 days dose administration)	Post Terminal Sacrifice (Sacrificed after 28 days post treatment)
Control (vehicle only) **G-1**	0	10	10	-
Low dose **G-2**	50	10	10	-
Intermediate dose **G-3**	100	10	10	-
High dose **G-4**	250	10	10	-
Recovery Control **G-5**	0	10	0	10
Recovery Intermediate Dose **G-6**	100	10	0	10

Table.2 Mean biochemistry data of female rats time: pretest (0th Day)

Groups	GLU (mg/dl)	SGOT (U/L)	SGPT (U/L)	BUN (mg/dl)	UREA (mg/dl)	SAP (U/L)	TP (g/dl)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	cholinesterase (U/L)
Control (G-1)	99.72 ± 0.95	85.87 ± 2.97	47.16 ± 3.54	18.04 ± 0.53	37.60 ± 1.32	117.63 ± 5.02	6.94 ± 0.50	140.80 ± 2.10	4.69 ± 0.50	98.90 ± 0.88	652.40 ± 4.30
Low Dose (G-2)	100.47 ± 1.10	87.11 ± 3.06	46.53 ± 4.67	18.04 ± 0.43	38.54 ± 0.81	117.36 ± 7.05	6.91 ± 0.42	140.60 ± 1.51	4.82 ± 0.42	99.00 ± 0.82	653.30 ± 4.99
Intermediate Dose (G-3)	99.92 ± 2.44	85.73 ± 4.09	46.48 ± 3.51	18.15 ± 0.66	38.40 ± 1.01	116.22 ± 3.29	6.59 ± 0.28	139.40 ± 1.96	5.12 ± 0.32	99.60 ± 1.07	652.10 ± 4.86
High Dose (G-4)	100.10 ± 1.12	86.68 ± 6.56	47.71 ± 2.83	18.62 ± 0.43	38.94 ± 1.14	116.08 ± 4.18	7.41 ± 0.41	140.82 ± 1.40	4.71 ± 0.37	99.77 ± 1.70	654.30 ± 5.77
Recovery control (G-5)	100.17 ± 0.86	87.48 ± 2.72	48.26 ± 2.58	18.35 ± 0.51	38.66 ± 1.03	116.21 ± 3.74	7.15 ± 0.52	140.51 ± 1.44	4.55 ± 0.32	99.66 ± 1.63	654.90 ± 3.73
Recovery Intermediate dose (G-6)	100.10 ± 1.12	87.16 ± 2.48	46.33 ± 2.15	18.33 ± 0.46	38.32 ± 1.18	115.71 ± 2.66	6.95 ± 0.53	140.50 ± 1.18	4.59 ± 0.23	99.60 ± 1.17	652.10 ± 3.96

Statistical analysis: ANOVA (p value:> 0.05)

Table.3 Mean biochemistry data of female rats

Parameters	Control (G-1)		Low Dose (G-2)		Intermediate Dose (G-3)		High Dose (G-4)	
	Day 45th	Day 91st	Day 45th	Day 91st	Day 45th	Day 91st	Day 45th	Day 91st
GLU (mg/dl)	77.30 ± 2.67	80.90 ± 5.26	81.70 ± 5.72	81.00 ± 6.67	84.60 ± 4.48	78.00 ± 4.85	79.40 ± 7.18	81.10 ± 5.17
SGOT (U/L)	82.70 ± 3.50	87.10 ± 4.48	84.50 ± 4.74	80.60 ± 4.33	85.60 ± 3.10	87.10 ± 6.26	83.40 ± 4.72	85.90 ± 9.83
SGPT (U/L)	41.50 ± 2.68	46.60 ± 1.58	43.60 ± 3.69	42.00 ± 3.40	45.40 ± 3.47	52.02±13.53	42.60 ± 5.13	54.00 ± 15.07
BUN (mg/dl)	19.63± 1.41	21.31 ± 1.50	21.82± 0.88	20.09 ± 1.57	20.93± 1.24	20.75 ± 1.47	20.56 ± 1.39	20.37 ± 1.31
UREA (mg/dl)	42.00 ± 3.02	45.60 ± 3.20	46.70± 1.89	43.00 ± 3.37	44.80± 2.66	44.40 ± 3.13	44.00 ± 2.98	43.60 ± 2.80
SAP (U/L)	103.50 ±4.74	101.50 ± 6.08	105.20 ±6.18	104.70±8.64	107.40 ±4.97	109.90±10.63	105.00± 6.62	105.10 ±7.81
T.P (g/dl)	7.48 ± 0.37	7.88 ± 0.21	8.09 ± 0.23	7.62 ± 0.29	7.92 ± 0.24	7.81 ± 0.21	7.84± 0.17	7.82 ± 0.19
Na^+ (mEq/L)	143.90 ± 2.77	144.40 ± 2.27	144.70 ± 1.49	142.80±2.44	144.70 ± 1.89	143.40± 1.96	144.20± 2.10	143.60 ± 2.27
K^+ (mEq/L)	4.34 ± 0.25	4.39 ± 0.16	4.37 ± 0.19	4.21 ± 0.16	4.27± 0.13	4.32 ± 0.19	4.29± 0.21	4.25 ± 0.16
Chloride (mEq/L)	101.30± 1.16	101.30± 1.16	102.50± 1.90	101.20±1.87	104.00± 2.31	102.50± 1.18	104.00± 1.33	102.40± 0.70
cholinesterase (U/L)	651.60± 3.24	652.40± 4.30	651.90± 4.07	656.10±6.72	649.00± 3.50	656.10± 6.72	649.70± 3.20	656.40± 6.87

Statistical analysis: ANOVA (p value :> 0.05), If p value <0.05 = Significant, If p value >0.05 = Non significant

Table.4 Mean biochemistry data of female rats (recovery group)Time: terminal sacrifice (119th day)

Animal group	GLU mg/dl	SGOT U/L	SGPT U/L	BUN mg/dl	UREA mg/dl	SAP U/L	T.P g/dl	Na^+ mEq/L	Potassium (mEq/L)	Chloride (mEq/L)	cholinesterase (U/L)
Recovery control (G-5)	78.80 ± 5.90	84.30 ± 3.33	44.80 ± 3.58	21.58 ± 1.19	45.70 ± 4.47	110.90 ± 7.02	7.76 ± 0.26	144.60 ± 2.46	4.16 ± 0.16	102.00 ± 1.15	653.10 ± 5.22
Recovery Intermediater dose (G-6)	82.90 ± 4.09	86.80 ± 7.98	47.80 ± 11.67	22.33 ± 1.57	46.70 ± 4.27	112.00 ± 7.09	7.79 ± 0.17	144.40 ± 1.90	4.24 ± 0.20	103.00 ± 1.25	652.10 ± 3.96

The analysis of biochemical parameters showed that all the parameters of low dose group- (G-2), intermediate dose group (G-3) and high dose group (G-40) were comparable to their control group(G-1), when evaluated on 0 day (pretest), 45th day (interim) of the study and all the parameters of low dose group (G-2) and intermediate dose group (G-3) were comparable to their control counterparts, when evaluated on 91st day (terminal sacrifice) of the study. However, a slight increase in SGOT, SGPT were noticed in the intermediate dose group and high dose group animals at terminal sacrifice *i.e.* day 91st and slight increase in SGOT, SGPT were noticed in the recovery intermediate dose group on terminal sacrifice *i.e.* 119th day. Reversibility of the toxic effects were seen in recovery intermediate dose animals (G-6) as all the biochemical parameters were comparable to their recovery control counterparts (G-5) as they fell within the accepted laboratory limits.

In conclusion the rat model is a key element in advancing biological research. The prevailing assumption that the responses to exercise obtained from rat models mimic human responses to exercise is supported by our study at least regarding most of the blood parameters measured. Rat demonstrated adequately reflected human responses to repeated exercise in blood parameters linked to various organs, tissues, functions, and diseases. Although it is plausible to anticipate similar blood profile changes in humans and rats after multiple exercise sessions. It is vital that future research directly compares rat and human responses to acute and chronic exercise in additional variables and sampling points. Our study highlights the various change in biochemimal parameters of female wistar rats over repeated exposure by Fomesafen by oral route through gavage. Under the conditions of this study, the repeated oral administration of 'Fomesafen

technical' in Female wistar rats at the dosage level of 50 mg/kg b.wt. for consecutive 90 days did not induce any observable toxic effects, alteration in blood biochemistry parameters when compared to its corresponding control group of animals.

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