Current Science International Volume : 04 | Issue : 02 | April-June | 2015
ISSN 2077-4435 Pages: 145-154

Acute Oral Toxicities of Three Pesticides Used in Egyptian Rice Farms to Albino Rats

El-Tawil, Mohamed F. and Marzouk E. M.A.

Department of Plant Protection, Faculty of Agriculture, Al-Azhar University, Nasr City, Cairo, Egypt.

ABSTRACT

The present study was carried out to determine the acute rat toxicity of three commercial pesticide formulations recommended against rice pests (i.e. Sumithion 50% EC as insecticide, Sayno 50% EC as herbicide and Fuji-one 40% EC as fungicide). All the tested formulations were administered orally to adult male and female albino rats and the median lethal doses (LD_{50} values) were determined after 24, 48, 72 and 96hours (hrs) post-treatment. The obtained results revealed that the oral LD_{50} values of aforementioned pesticide formulations on adult male and female rats were (1166.983, 1253.818), (895.698, 966.445) and (966.445, 895.698) mg/Kg body weight (b.w.) after 24 hrs, respectively. Moreover, the 48hrs oral LD_{50} values of the tested pesticide formulations mentioned above were (1012.383, 1081.599), (721.09, 838.617) and (721.09, 781.164) mg/Kg b.w., respectively. No rat mortality was occurred after 48hrs. Therefore, the LD_{50} values after 72 and 96 hrs were the same as determined at 48hrs. The obtained results indicated that the male rats were more sensitive to these toxicants than females. Also, the acute toxicities of these commercial pesticide formulations seemed to be more toxic than their reported toxicities which based on active ingredients. It was surprising that, the candidate fungicide and herbicide exhibited higher acute toxicity to rats than the Sumithion insecticide.

Key words: Pesticide Formulation - LD_{50} - Albino Rats- Rice.

Introduction

The toxicity of any chemical can be measured in several ways, but generally human toxicity is estimated based on test results on rats and other animal models. Any substance that is poisonous to rat is not necessarily equally poisonous to humans or other animals. Some pesticides are fatal after one lethal dose (acute toxicity); others can be dangerous after sublethal, repeated doses (chronic toxicity). One simple measure of toxicity use bioassays to measure death rates in order to quantify the effect of the toxin. This measure is commonly known as a lethal dose 50 (LD_{50}). The LD_{50} is usually an initial screening step in the assessment and evaluation of the toxic characteristic of a substance. Therefore, a pesticide LD_{50} normally provides information on health hazards likely to arise from short-term exposure and serve as a basis for labeling and classification and also helpful in establishing a dosage regimen in sub-chronic and chronic studies (Chandra *et al.,* 2014).

Pesticides, in general, perform their activity by acute toxicity to the target organisms (Matsunaka, 1992) and the simplest acute toxicity study employs LD_{50} value determination. The toxicity of chemicals has been classified according to their oral LD_{50} values, giving simple approximate expression of the degree of toxicity (Matsumura, 1995).

Fenitrothion belongs to the organophosphorus insecticides, it is a contact insecticide and selective acaricide of low ovicidal properties (Spencer, 1981) and it is considered a cholinesterase inhibitor (Kidd and James, 1991). The commercial formulation of fenitrothion insecticide (Sumithion 50% EC) is used for controlling chewing, sucking, and boring insects in cereals, soft fruit, tropical fruit, vines, rice, sugar cane, vegetables, turf, and forestry. Also used as a public health insecticide for control of household insects (flies, cockroaches, and other insects) by application to breeding sites; for control of flies in animal houses; for control of stored product insect pests; for control of mosquito larvae (as a vector control agent for malaria); and for control of locusts (Anonymous, 2003).

Herbicides can cause deleterious effects on organisms and human health, both by their direct and indirect actions (Kortekamp, 2011 and Zeliger, 2011). With respect to the toxicity, some herbicides pose major concerns when applied in regions close to water resources due to their highly toxic potential to many aquatic organisms (Polard *et al*., 2011). The contamination of aquatic environments by herbicides has been characterized as a major world concern. This aquatic contamination is due to the use of these products in the control of aquatic plants, leachate and runoff of agricultural areas (Ying and Williams, 2000).

Corresponding Author: Marzouk, Emad M.A., Department of Plant Protection, Faculty of Agriculture, Al-Azhar University, Nasr City, Cairo, Egypt.
E-mail: emad_marzouk2000@yahoo.com

The commercial formulation of thiobencarb herbicide (Sayno 50% EC) is used for Pre-emergence to early post-emergence control of *Echinochloa, Leptochloa, and Cyperus spp.* and other monocotyledonous and annual broad-leaved weeds in direct-seeded and transplanted rice, at 3-6 kg ha^{-1} (Anonymous, 2003).

Fungicides are extensively used in industry, agriculture, the home and garden. Fungicides vary enormously in their potential for causing adverse effects in humans. According to the EPA manual, Recognition and Management of Pesticide Poisoning, most fungicides currently in use are unlikely to cause frequent or severe systemic poisonings. Apart from poisonings that affect the body generally, fungicides have probably caused disproportionate numbers of irritant injuries to skin and mucous membranes, as well as some dermal sensitization (Larry *et al*., 2001 and Morgan, 1999). The acute toxicity of fungicides to humans is generally considered to be low, but fungicides can be irritating to the skin and eyes. Inhalation of spray mist or dust from these pesticides may cause throat irritation, sneezing and coughing (Pesticide Safety Fact Sheet, 2009).

The commercial formulation of isoprothiolane fungicide, Fuji-one 40% EC is used to control the following pathogens and insect pests, at 400-600 g ha^{-1} (foliar spray), 3.0-6.0 g/nursery box (spreading treatment), 3.6-6.0 kg ha^{-1} (submerged treatment), 360-600 g $tree^{-1}$ (soil incorporation): *Pyricularia oryzae, Helminthosporium sigmoideum, Fusarium nivale* on rice; *Rosellinia necatrix* on pome fruit, stone fruit and grapes; Delphacidae (planthoppers) on rice. Also used in rice to accelerate rooting, promote root elongation and control non-parasitic damping-off (Anonymous, 2003).

In agriculture, the use of pesticide has been the dominant form of pest management since the 1950s to kill pest organisms including insects, weeds, fungi and nematodes. In recent times, use of pesticides in rice farming has increased rapidly and this scenario contributes significantly towards adverse effects on human health and environment (Ahmad *et al.,* 2014 and Snelder *et al*., 2008). In rice farming, pesticide application has been promoted among farmers in developing countries to increase their productivity and enhance economic potential for farm households (Ecobichon, 2001). A proportion of the pesticide that is not absorbed by the plants will be moved and transferred to the environment through wind, water and soil. Depending on the physicochemical properties, it can be transported thousands of miles away and can infiltrate into meat, milk, human blood, animal and plants, which may result in serious health implications to humans and the environment. In addition, continuous pesticide application may put farmers' health at risk, with pesticides being dispersed, spilled or leaked and entering the human body either directly or indirectly. In the literature, there is vast evidence that pesticides do pose a potential risk to humans (Igbedioh, 1991), and other life forms as well as unwanted side effects to the environment (Zhang *et al.,* 2010). In relation to that, various reports of ill health associated with those applying pesticides has been reported by Food and Agricultural Organisation (FAO, 2014).

The LD_{50} values are generally expressed on the basis of active ingredient. If a commercial product is formulated to contain 50 percent active ingredient, it would take two parts of the material to make one part of the active ingredient. In some cases, other chemicals mixed with the active ingredient for formulating the pesticide product may cause the toxicity to differ from that of the active ingredient alone (Norman *et al*., 2014). Moreover, because of determining the toxicity of a pesticide to humans is not easy, since humans cannot be used as the test subject, other animals, such as rats, are used (Clyde *et al*., 2012). The results of these toxicity tests are used to predict the safety of the new chemical to humans and human toxicity from exposure to small doses for long periods of time (Norman *et al*., 2014).

Thus, the present work was undertaken to evaluate the acute oral toxicity of three rice farming pesticide formulations used by rice farmers in Egypt i.e. Sumithion 50% EC (fenitrothion insecticide), Sayno 50% EC (thiobencarb herbicide) and Fuji-one 40% EC (isoprothiolane fungicide) through the determination of their LD_{50} values on adult male and female albino rats.

Materials and Methods:

A- Pesticides:

1. Sumithion 50% EC (fenitrothion, organophosphorus insecticide):

IUPAC Chemical name:

O,O-dimethyl *O*-4-nitro-*m*-tolyl phosphorothioate.

The commercial formulation of fenitrothion insecticide, Sumithion 50% EC was obtained from Sumitomo Corporation Cairo Company.

2. Sayno 50% EC (thiobencarb, thiocarbamate herbicide):

IUPAC Chemical name:

S-4-chlorobenzyl diethylthiocarbamate.

The commercial formulation of thiobencarb herbicide, Sayno 50% EC was obtained from Egypt for Fertilizers and Chemicals Company (EFC Co.).

3. Fuji-one 40% EC (isoprothiolane, dithiolane fungicide):
IUPAC Chemical name:
di-isopropyl 1,3-dithiolan-2-ylidenemalonate.

The commercial formulation of isoprothiolane, fungicide, Fuji-one 40% EC was obtained from Shoura Chemicals Company, Cairo.

All commercial formulations of pesticides used were obtained from the Research Institute of Plants Protection, Dokki, Giza.

B-Experimental animals:

Albino rats (Wister strain) were obtained from Helwan Farm of Egyptian Organization for Vaccine and Biological Preparations. Male and female rats ranging in weight from 180-220 gm were used for experimentation. Rats were fed on standard chow diet obtained from El-Salam Factory for Dry Ration-El-Marg - Egypt; and water was freely provided *ad libitum.* Male and female rats were separated and placed in stainless steel cages, with different capacities i.e. 35 x 25 x 20 cm and 30 x 20 x 20 cm, (5 animals group-caged by dose and by sex). All animals were allowed for acclimatization to the laboratory conditions for 10 days prior to dosing. Temperature 22ºC ± 3, relative humidity 30 - 70%and 12 hours light/dark cycle. At the beginning of experiments, unhealthy rats were excluded; and animal body weight was measured to the nearest gram. The total numbers of rats used in the present studies were 105 adult male and 105 adult female rats.

C-Experimentation:

The acute oral LD_{50} values of Sumithion 50% EC, fenitrothion insecticide, Sayno 50% EC, thiobencarb herbicide, and Fuji-one 40% EC, isoprothiolane fungicide, (i.e. three compounds) on adult male and female rats were determined. The total number of rats for each sex was divided as: 3 compounds × 6 doses for each compound plus the control (i.e.7 treatments) × 5 rats for each treatment = 105 rats. Prior to dosing, animals were deprived of food for 12-15 hrs overnight but given free access to water. Each pesticide was dissolved in corn oil (1 ml/kg b.w. rat), while untreated animals were given 1 ml corn oil/kg b.w..

Oral dosing was carried out using a glass syringe attached to a curved stainless steel animal intubation needle with spherical ball tip. Doses were prepared shortly prior to administration.

The tested doses of Sumithion were 0, 600, 900, 1200, 1500 1800 and 2100 mg/kg body weight (b.w.). In the case of Sayno and Fuji-one, the doses were 0, 400, 600, 800, 1000, 1200 and 1400 mg/kg b.w. for both male and female rats. After toxicant administration, the animals were provided, with free access to food and water, and are observed at least once during the first 30 minutes, periodically during the first 24 hours (with special attention during the first 4 hours), and daily thereafter and the mortality rate was recorded for 4 days. The LD_{50} values were determined according to the "Probit analysis" technique described by **Finney (1971).**

All experiments of the present study were conducted at the laboratories of pesticides research, Department of Plant Protection, Faculty of Agriculture, Al-Azhar University, Nasr City, Cairo, Egypt.

Results and Discussion

The types of toxicity tests that are routinely performed by pharmaceutical manufacturers in the investigation of a new drug involve acute, sub - acute and chronic toxicity. Acute toxicity is involved in estimation of LD_{50} values. Determination of acute oral toxicity is usually an initial screening step in the assessment and evaluation of the toxic characteristics of all compounds (Shetty *et al*., 2007). Pesticides may be classified by target organism, chemical structure and physical state, etc. Chemical structures differ within categories as well as between categories. Thus, toxicity to target and non-targeted species can vary widely within each group. Rampant use of pesticides in agricultural products continues to risk the life of the common man. Thus, it is very important to know the LD_{50} value of the pesticide before using it in the fields (Raj *et al*., 2013).

It was observed that all rats had signs of intoxication, which varied in severity according to the dose administered. The animals showed toxicity signs of hyperexcitibility, profuse salivation, tremors, burrowing behavior, frequent maturation, diarrhea, hunched back, muscular incoordination, weakness, altered gait, startle response, writhing movements of neck, violent twisting movements sometimes lifted from the body from floor, labored breathing, gasping, convulsions and death. There was full recovery of surviving rats (Lyaniwura and Okonkwo, 2004).

The determined LD_{50} values are shown in tables (1 and 2) and Figs.
(1 and 2). Generally, it was found that all rat mortalities occurred within 48 hrs from pesticides treatment. The LD_{50} values of an organophosphorus insecticide fenitrothion (Sumithion 50% EC) for male rats were 1166.983 mg/kg b.w. after 24 hrs and 1012.383 mg/kg after 48 hrs post treatment. While the values of LD_{50} for female rats were 1253.818 mg/kg after 24hrs and 1081.599 mg/kg after 48 hrs post treatment, which indicated clearly that fenitrothion insecticide was more toxic to male rats than to female rats. These findings are coincided with

those obtained previously by other investigators, the acute oral LD_{50} values for male and female rats were 1700 and 1720 mg/kg, respectively (Anonymous, 2003). It was reported that the acute oral LD_{50} values of fenitrothion to rats ranges between 250-800 mg/kg (OHS, 1993). Worthing and Walker (1987) recorded an oral LD_{50} value of fenitrothion of 800 mg/kg for female rats. In addition, Mikami *et al.* (1977) estimated the acute oral of fenitrothion in corn oil on male and female rats. The LD_{50} value was 660 mg/kg b.w. for males and 1050 mg/kg b.w. for females. Consequently, the obtained LD_{50} values of fenitrothion are in agreement with that of Rosival *et al*. (1976) and Kadota *et al.* (1972). They found that the acute oral LD_{50} values of fenitrothion insecticide were 700 and 800 mg/kg for male and female rats, respectively. Whereas Benes and Cerna (1970) and Gaines (1969) reported that the LD_{50} values of fenitrothion to adult male rats were 940 and 740 mg/kg, respectively, when administered orally.

It have been indicated that the acute toxicity of fenitrothion to mammals is considered to be low due to its high metabolic rate (Gallo and Lawryk, 1991). Fenitrothion is more rapidly broken down and does not persist in areas where they are used and it was developed in place of parathion for its highly selective toxicity to insects over humans and animals (Hayes, 1982 and Spencer, 1981).

On the basis of the obtained LD_{50} values shown in Tables (1 and 2) and Figs. (1 and 2) the LD_{50} values for thiocarbamate herbicide thiobencarb (Sayno 50% EC) were 895.698 and 721.09 mg/kg at 24 and 48 hrs intervals after dosing of male rats, respectively; while the LD_{50} values were 966.445 and 838.617 mg/kg after 24 and 48 hrs of dosing for female rats, respectively, which indicated that thiobencarb herbicide was more toxic to male than female rats. These findings are in agreement with those obtained previously by EFSA (2013) who found that the acute oral LD_{50} values of technical thiobencarb 96% and 99.2 % were 1033 and 920 mg/kg for male rats and 1130 and 960 mg/kg b.w. for females, respectively. In addition, thiobencarb acute oral LD_{50} values in rats ranged from 920 to 980 mg/kg b.w. (Louisiana Suggested Weed Management Guide, 2012). According to the Anonymous (2003), WSSA (1983) and Nishimura (1985) the acute oral LD_{50} values of thiobencarb to male and female rats were 1033 and 1130 mg/kg with lower and upper ranges of 924-1155 mg/kg and 1033-1247 mg/kg, respectively.

However, the present results are in contradiction with those obtained by MSDS (2014) and Bayer Crop Science (2010) who demonstrated that the acute oral LD_{50} values of thiobencarb were 1414 and 1231 mg/kg for male and female rats, respectively.

On the other hand, in accordance with the obtained LD_{50} values shown in Tables (1 and 2) and Figs. (1 and 2) the LD_{50} values for dithiolane fungicide isoprothiolane (Fuji-one 40% EC) were 966.445 mg/kg at 24hrs after dosing and 721.09 mg/kg at 48 hrs after dosing for male rats. While they were 895.698 mg/kg at 24 hrs and 781.164 mg/kg at 48 hrs after treatment for female rats which indicated that males generally were more sensitive than females. These findings are in agreement with those obtained previously by (Agro-care Chemical Industry Group Limited, 2002 and CAPL, 2009) who found that the acute oral LD_{50} values of isoprothiolane were 1190 and 1340 mg/kg for male and female rats, respectively. SANS (2010); Sigma-Aldrich (2010) and Farm Chemicals Handbook (1991) found that the acute oral LD_{50} value of isoprothiolane for rats was 1190 mg/kg .

It was reported that isoprothiolane, trade name – Fuji one, a related dithiolane fungicide, belong to organosulphur group of compound is also used as an insecticide (Selvi Arul *et al*., 2013). These are mainly used to control rice blast disease and to reduce the population of brown plant hopper and leaf hopper in rice plants (Uesugi, 2001). This fungicide has adverse effects on humans resulting in eye irritation, serious eye damage and severe acute toxicity. Isoprothiolane residues in water and soil are of concern as their uptake can lead to the accumulation of primary products (Fushiwaki *et al*., 1993), and results in the toxic effect to the non target species such as humans through food chain (Uesugi, 2001).

It was surprising that, the candidate fungicide and herbicide exhibited higher acute toxicity to rats than the Sumithion insecticide. It have been reported that several factors influence acute LD_{50} values including sex of the animals used and formulation of pesticide (Coombs *et al.,* 1979); route of exposure is critical in assessing the potential of a toxicant. Some of these factors probably contributed to the variation of the oral LD_{50} values between male and female rats.

As shown in Tables (1 and 2) and Figs. (1 and 2) the sex differences in susceptibility to pesticides in rats have been well demonstrated. In general, male rats were more sensitive than females. The published literature records cases when male rodents are more sensitive to xenobiotics than females. While these data suggest that the sexes are not equally sensitive to all of the pesticides tested, no clear cut generalizations about sex sensitivity could be made; although females were often more sensitive, this was not always true (Rispin *et al*., 2000). In a comparison of male and female rat oral and dermal LD_{50} values, pesticides showed significant differences in sensitivity in male and female rats (EPA, 1991). Moser *et al*. (1998) and Timbrell (1991) notes that chlorpyrifos is more acutely toxic to male rats than to females. This may be due to differences in the way that vital organs react to toxins can also have a significant impact on overall toxicity. The insecticides such as aldrin and heptachlor are metabolized more rapidly to the toxic epoxide forms in male rats. These pesticides demonstrate a lower toxicity in the female rat.

In addition, metabolic differences due to gender can also have an effect on sensitivity for acute effects; Sipes and Gandolfo (1991) suggested that because male rats metabolize most foreign compounds faster than females, one would expect the biological half-life of most xenobiotics to be longer in the female than the male rat. However, if a metabolite or intermediate is responsible for the toxic response, male rats would be expected to show the greater susceptibility.

Certain organophosphate pesticides are detoxified by glutathione S-transferases. However, cytochrome P450 (CYP) mediated metabolism can also cause formation of reactive metabolites. Female rats are known to have 10 - 30% less total CYP as compared with male rats (Kedderis and Mugford, 1998). Conjugative enzymes, i.e. sulfotransferases, glutathione S-transferases and glucuronyltransferases, also play a role in detoxification. Sex-dependent differences have also been found in expression of these enzymes. When such sex-dependent differences are seen, it is generally the male rats which have higher enzyme activities. For example, glutathione protects tissues against electrophilic attack by xenobiotics. DeBethizy and Hayes (1994) noted that glutathione conjugating activity toward dichloronitrobenzene is two- to three-fold higher in male than female rats. Conjugation of xenobiotics may not always lead to more rapid excretion of the conjugated metabolite. In fact, some compounds are toxic only after conjugation with glutathione. Glutathional conjugates which are implicated in nephrotoxicity would be likely to; show greater toxicity in males than females.

In accordance with the obtained LD_{50} values, it was reported that the formulations of pesticides affects their toxicities (El-Sebae *et al.,* 1978) and the pesticide formulations seem to be more toxic than their active ingredients alone (El-Sebae *et al.,* 1982). Since the technical grade is usually formulated (mixed with carriers, solvents, etc.) for use in commercial pest control, the toxicity of these other ingredients must be taken into consideration when assessing the toxicity of a formulated product (Williamson, 1989). The WHO (1991) emphasized that the final toxic classification of any pesticide is related to its formulation form which appears to enhance pesticide toxicity. This may be due to the effects of additives such as organic solvents and surfactants in the formulation form of pesticides which increase its penetration through its target tissue of organisms causing more toxicity than the pure active ingredient materials of the pesticides (El-Sebae *et al.*, 1978, 1982; WHO, 1991 and Abou-Zeid *et al.,* 1993).

Consequently, these findings may be due to the fact that many formulations contain adjuvants (stabilizers, penetrants, surfactants) that may have significant irritating and toxic effects in addition to the primary herbicide. A number of premixed products may be combination formulations with additional active ingredients that are more toxic than the principal herbicide. Therefore, it is important to read the label to identify each active ingredient and its associated toxicities. Good hygienic practice should not be disregarded because only the primary pesticide is reported to have a high LD_{50} in laboratory animals (Roberts *et al*. 2009 and Eddleston *et al*. 2002).

Finally, it will be needed to carry out research aims at more effective methods (e.g. Subacute, subchronic and chronic toxicity studies) to prevent and/or reduce the deleterious effects of such compounds on the environment, the biota potentially exposed, and especially to human health (Marin-Morales *et al.,* 2013). Additionally, with further expansion and intensification in rice production, extended research on pesticide use among farmers is then essential. This in turn may help in adapting safe pesticide management practices in rice farming (Ahmad *et al.,* 2014).

Table 1: The acute oral LD_{50} values of tested pesticide formulations for male albino rats after 24 and 48 hrs of treatment.

Duration	24 hrs				48 hrs			
	LD50 values (mg/kg)	Confidence limits (mg/kg)		Slope	LD_{50} values (mg/kg)	Confidence limits (mg/kg)		Slope
pesticides		Lower	Upper			Lower	Upper	
Fenitrothion	1166.983	950.292	1389.28	3.185	1012.383	935.511	1087.573	3.823
Thiobencarb	895.698	722.505	1139.334	3.166	721.09	660.841	783.373	3.240
Isoprothiolane	966.445	796.276	1256.812	2.958	721.09	660.841	783.373	3.240

Table 2: The acute oral LD50 values of tested pesticide formulations for female albino rats after 24 and 48 hrs of treatment.

Duration	24 hrs				48 hrs			
	LD50 values (mg/kg)	Confidence limits (mg/kg)		Slope	LD50 values (mg/kg)	Confidence limits (mg/kg)		Slope
Pesticides		Lower	Upper			Lower	Upper	
Fenitrothion	1253.818	994.336	1558.004	3.660	1081.599	991.223	1175.028	3.239
Thiobencarb	966.445	796.276	1256.812	2.958	838.617	672.097	1124.164	3.620
Isoprothiolane	895.698	722.505	1139.334	3.166	781.164	637.84	971.064	3.134

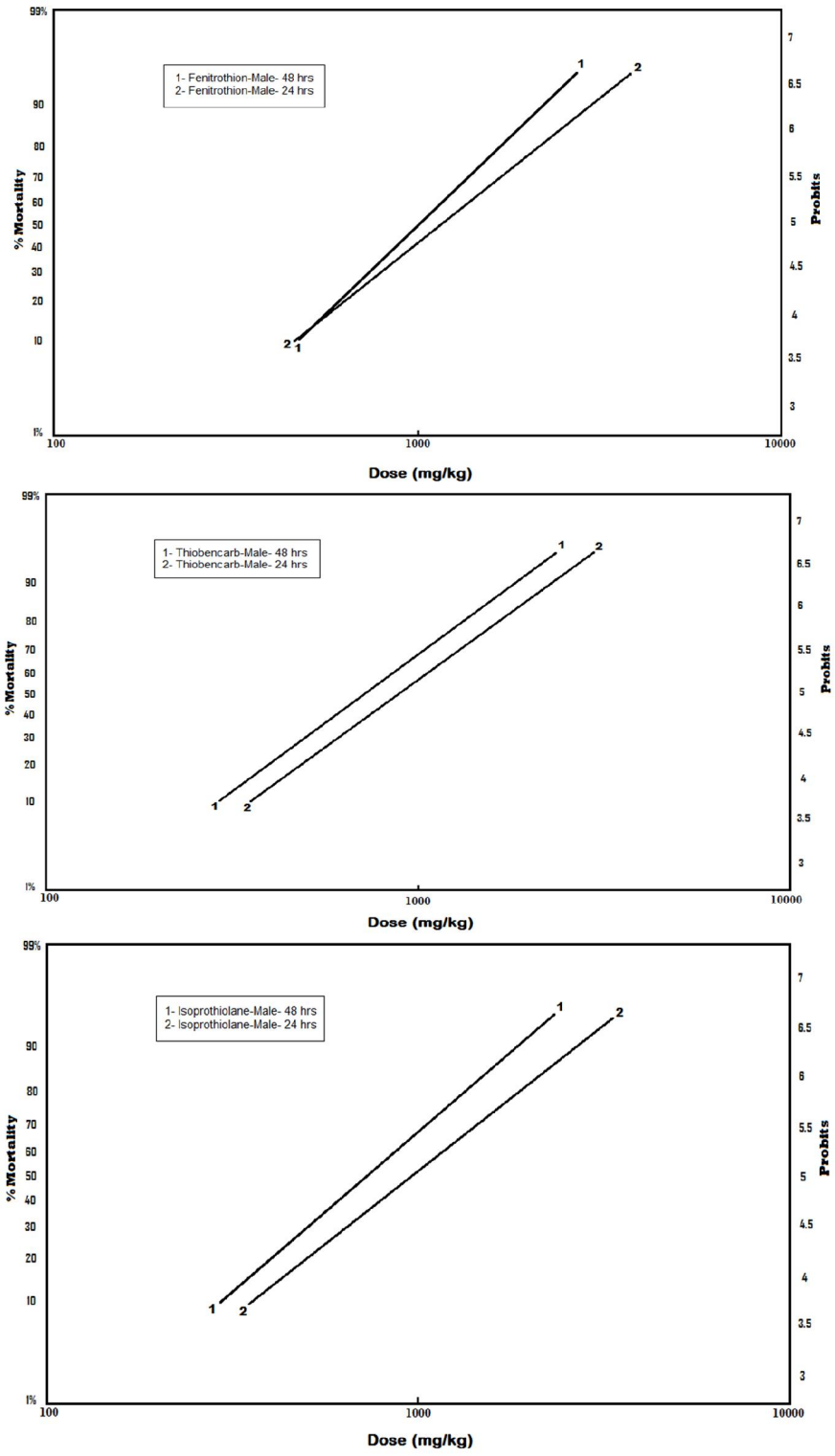

Fig. 1: Toxicity lines of median lethal doses (LD_{50} values) of the tested pesticides on adult male albino rats dosed orally at different times.

1: Ld-p (Log dose – probit) line after 48,72 and 96 hrs.

2: Ld-p line after 24 hrs.

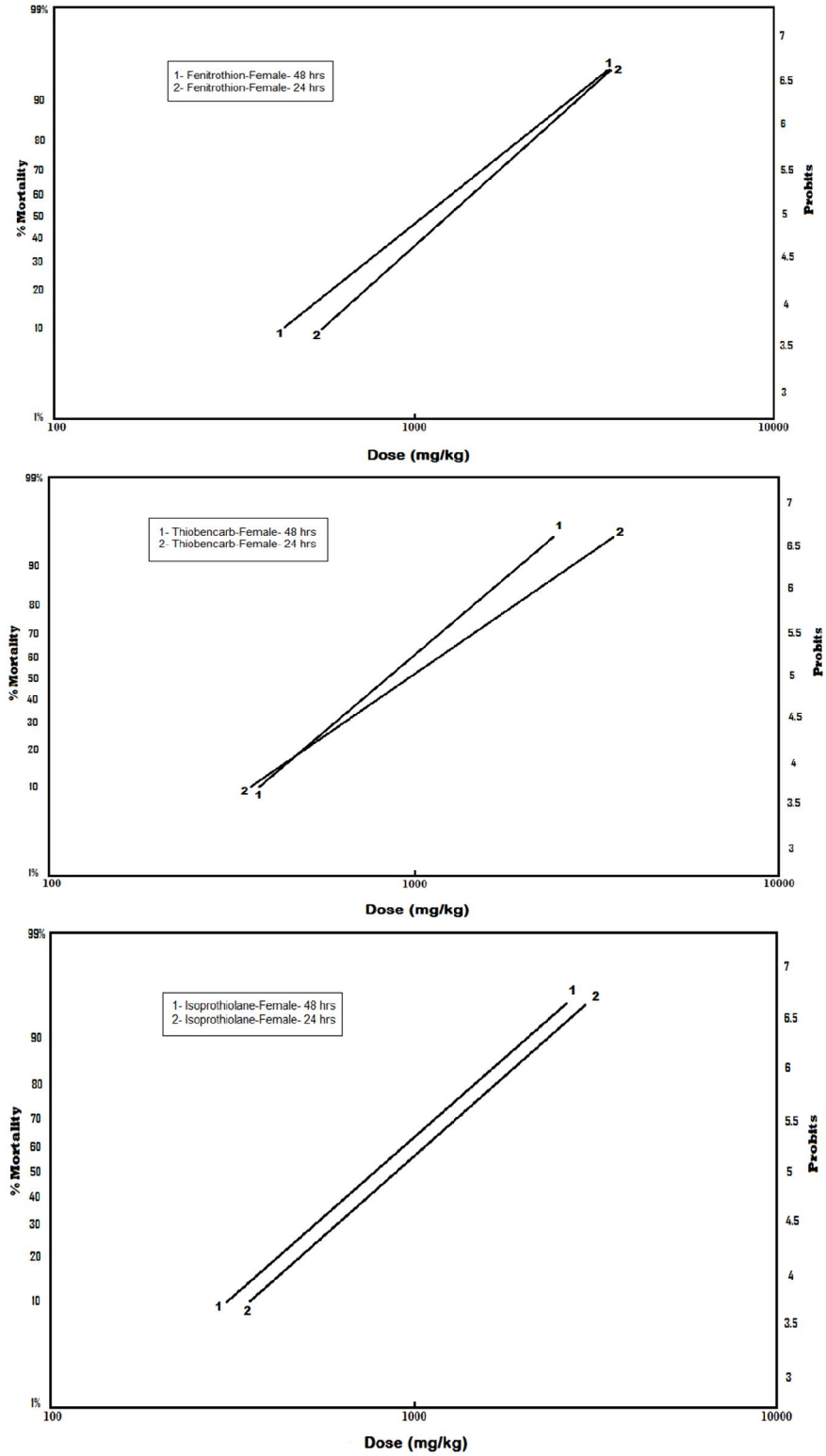

Fig. 2: Toxicity lines of median lethal doses (LD_{50} values) of the tested pesticides on adult female albino rats dosed orally at different times.

1: Ld-p (Log dose – probit) line after 48,72 and 96 hrs.

2: Ld-p line after 24 hrs.

References

Abou-Zied, M.M., G. El-Baroty, E. Abdel-Rahim, J. Blankate, C. Dary, A.H. El-Sebae and M.A. Saleh, 1993. Malathion disposition in dermally and orally treated rats and its impact on the blood serum acetylcholinesterase and protein profile. J. Environ. Sci. Health 828(4): 413-430.

Agro-care Chemical Industry Group Limited, 2002.Isoprothiolane, fungicides.

Ahmad M. I., N. A. Ahmad, S. A. Muhammad and N. Esa, 2014. A Survey on Use, Hazards and Potential Risks of Rice Farming Pesticides in Permatang Keriang, Pulau Pinang (Malaysia).International Journal of Scientific and Research Publications, Volume 4, Issue 10: 1-11.

Anonymous, 2003. The pesticide Manual, Version:3, Thirteen Edition, BCPC (British Crop Protection Council). http://www.bcpc.org/epm.

Bayer Crop Science, 2010. Material Safety Data Sheet. Saturn® EC Rice Herbicide.

Benes V. and V. Cerna, 1970. Contribution to the toxicological evaluation of fenitrothion and its residues. In: Deichmann WB, Radomski JL and Penalver RA, ed. Proceedings of Pesticide Symposia. Inter-American Conferences on Toxicology and Occupational Medicine, Miami, Florida, Halas & Ass., inc., pp. 219-222.

CAPL, 2009. Central Agricultural Pesticides Laboratory. Optimizing Pesticide Use The guidance program of CAPL.

Chandra M.; J. Raj, T. Das Dogra, A. C. Rajvanshi and A. Raina, 2014. Determination of median lethal dose of triazophos with DMSO in wistar rats. Asian J Pharm Clin Res, Vol 7, Issue 4, 64-67.

Clyde L. O., J. R. Hygnstrom, E. C. Bauer and P. J. Hansen, 2012. Managing Pesticide Poisoning Risk and Understanding the Signs and Symptoms. Division of the Institute of Agriculture and Natural Resources at the University of Nebraska–Lincoln cooperating with the Counties and the United States Department of Agriculture.

Coombs A.D., B.I. Carter and R. W. Hend, 1979. Toxicity Studies of the Insecticide WL 43467. Summary of Results of Preliminary Experiments. Shell Research (TLGR. 0104.76), Sittingbourne.

DeBethizy J.D. and J.R. Hayes,1994. Metabolism: A Determinant of Toxicity, in Principles and Methods of Toxicology. A.W. Hayes, Editor. Raven Press, N.Y. Third Edition 1994.

Ecobichon D. J., 2001. Pesticide use in developing countries. Toxicology, 160, 27-33.

Eddleston M., M. Rajapakshe, K. D. Roberts, M. H. Reginald, R. Sheriff, W. Dissanayake and N. Buckley, 2002. Severe propanil [N-(3,4-dichlorophenyl) propanamide] pesticide self-poisoning. J. Toxicol. Clin. Toxicol.;40 (7): 847-854.

EFSA, 2013. Setting of a new MRL for thiobencarb in rice. European Food Safety Authority (EFSA) Journal; 11(10):3427.

El-Sebae A. H., N. S. Ahmed and S.A. Soliman, 1978. Effect of pre-exposure on acute toxicity of organophosphorus insecticides to white mice. J. Env. Sci. Health B,B: 4-24.

El-Sebae A. H., A. S. Dawood, E. Enan, S. A. Soliman and O.H. Enan, 1982. Selective toxicity of synthetic pyrethroids and their combinations to white mice and cotton leafworm. In: proceedings of the 5th IUPAC chemistry of pesticides conference. Japan.

EPA (Environmental Protection Agency, 1991. Comparison of Male and Female Rat Oral and Dermal LD_{50} Values in OPP'S One-Liner Data Base. Clement International Corporation.

FAO (Food and Agricultural Organisation), 2014. http://www.fao.org/ agriculture [Accessed May, 17th 2014].

Farm Chemicals Handbook, 1991. Pg. C174. Isoprothiolane Toxicity Data With Reference, LookChem.com.

Finney, D.J., 1971. Probit analysis . Cambridge University Press, London, 450 p.

Fushiwaki Y., T. Hamamura, A. Hasegawa and K. Urano, 1993. Environmental Pollution by Pesticides From Golf Courses in Kanagawa Prefecture. Japanese Journal of Toxicology and Environmental Health [JAP. J. Toxicol. Environ. Health]. Vol. 39, no. 6, pp. 543-548.

Gaines, T.B., 1969. Acute toxicity of pesticides. Toxcol. Appl. Pharmacol. 14: 515-534.

Gallo M. A. and N. J. Lawryk, 1991. Organic phosphorus pesticides. In Handbook of Pesticide Toxicology. Hayes, W. J., Jr. and Laws, E. R., Jr., Eds. Academic Press, New York, NY, 5-3.

Hayes W.J., 1982. Pesticides Studied in Man. Williams and Wilkins. Baltimore, London.

Igbedioh S.O., 1991. Effects of agricultural pesticides on humans, animals and higher plants in developing countries. Arch Environ Health;46:218.

Kadota T., M. Kagoshima, H. Yamazaki and J. Miyamoto, 1972. Acute oral, subcutaneous and dermal toxicities of Sumithion technical in mice and rats. Research Department, Pesticides Division Sumitomo Chemical Company, Japan. Report date: September 30, 1972. Unpublished [WE; sub: A3162/3, Box 64, Vol 2][also SU; sub: 1602, A3162/1, Box 155, Vol 2].

Kedderis G.L. and C.A. Mugford, 1998. Sex-Dependent Metabolism of Xenobiotics. CIIT Activities. Chemical Industry Institute of Toxicology.

Kidd, H. and D. R. Eds. James, 1991. The Agrochemicals Handbook, Third Edition. Royal Society of Chemistry Information Services, Cambridge, UK,5-14.

Kortekamp A., 2011. Herbicides and Environment. Kroatia, 760 p.

Larry D. Schulze, L. O. Clyde. and E. F. Vitzthum, 2001. Signs and Symptoms of Pesticide Poisoning. University of Nebraska Cooperative Extension EC97-2505-A.

Louisiana Suggested Weed Management Guide, 2012. Relative Toxicity of Herbicides to Mammals. pp., 199-203.

Lyaniwura T.T. and C. A. Okonkwo, 2004. The acute intraperitoneal toxicity of cypermethrin. Veterinary and Human Toxicology 46(2): 91-92.

Marin-M., M. Aparecida, B. de C. Ventura-Camargo and M. M. Hoshina, 2013. Toxicity of Herbicides: Impact on Aquatic and Soil Biota and Human Health. Herbicides - Current Research and Case Studies in Use. http://dx.doi.org/10.5772/55851.

Matsumura F., 1995. Toxicology of insecticides Plenum Press, New York 105-115: 403-404.

Matsunaka S., 1992. Proceedings of the First International Weed Control Congress, Melbourne. Biochemistry of herbicides and their relationships with animal toxicity.

Mikami N., H. Kohda and H. Suzuki, 1977. Toxicity study of S-methylfenitrothion. Institute for Biological Sciences, Japan. Report date: April 24, 1977. Unpublished [SU; sub: 1603, A3162/1, Box 159, Vol 1].

Morgan D. P., 1999. Recognition and Management of Pesticide Poisonings. Fifth Edition. Document No. EPA735-R98-003. Supt. of Documents, U.S. Government Printing Office, Washington, D.C. 20402-9325. http://npic.orst.edu/rmpp.htm.

Moser V. C.; S. M. Chanda, S. R. Mortensen and S. Padilla, 1998. Age- and Gender-Related Differences in Sensitivity to Chlorpyrifos in the Rat Reflect Developmental Profiles of Esterase Activities. Toxicological Sciences 46, 211-222.

MSDS, 2014. Material Safety Data Sheet. MSDS Kenso Agcare Pluto 800 Herbicide.

Nishimura N., 1985. Acute toxicity study of Benthiocarb by oral and dermal administration in the rat. Unpublished study prepared by Bozo Research Center, Inc. (U.S. EPA MRID 42130701).

Norman O. N., F. M. Fishel and M. Mossler, 2014. Toxicity of Pesticides. U.S. Department of Agriculture, UF/IFAS Extension Service, University of Florida, IFAS, Florida A & M University Cooperative Extension Program, and Boards of County Commissioners Cooperating. Nick T. Place, dean for UF/IFAS Extension. Visit the EDIS website at: http://edis.ifas.ufl.edu.

OHS, 1993. Occupational Health Services, Inc. Database. MSDS for Acephate. OHS Inc., Secaucus, NJ.

Pesticide Safety Fact Sheet, 2009. Potential Health Effects of Pesticides. College of Agricultural Sciences. Agricultural Research and Cooperative Extension Pesticide Education Program. The Pennsylvania State University 2009. www.pested.psu.edu/ on the Web.

Polard T., S. Jean, L. Gauthier, C. Laplanche, G. Merlina, J.M. Sánches-Pérez and E. Pinelli, 2011. Mutagenic impact on fish of runoff events in agricultural areas in south west France. Aquatic Toxicology, v.17, p. 126-134.

Raj J., M. Chandra, T.D. Dogra, M. Pahuja and A. Raina, 2013. Determination of median lethal dose of combination of endosulfan and cypermethrin in wistar rat. Toxicol Int;20(1):1-5.

Rispin A., H. Podall and W. Meyer, 2000. Gender Sensitivity of Xenobiotics. Up-and-Down Procedure Peer Panel Report Appendix P-1.

Roberts D. M., R. Heilmair, N. A. Buckley, A. H. Dawson, M. Fahim, M. Eddleston and P. Eyer, 2009. Clinical outcomes and kinetics of propanil following acute self-poisoning: a prospective case series. BMC Clin. Pharmacol.; 9:3.

Rosival L., M. Vargova, J. Szokolayova and K. Cerey, 1976. Contribution to the toxic action of S-Methyl-Fenitrothion. Pesticide Biochem & Physiol 6: 280-286 [SU; sub: 1603, A3162/1, Box 159,Vol 1].

SANS, 2010. SANS 10228-E: The identification and classification of dangerous goods, Annex E: Alphabetical list of pesticides (technical): Toxicity, Edition 5.

Selvi A. A., N. K. Rastogi and H. K. Mononmoni, 2013. Degradation of isoprothiolane by a defined microbial consortium using response surface methodology, Journal of Environmental Biology, Vol.34, 545-554.

Shetty A., D. Shyamjith, and M.C. Alwar, 2007. Acute toxicity studies and determination of median lethal dose. Current Science, 93(7): 917-920.

Sigma-Aldrich, 2010. Material Safety Data Sheet, Version 4.2 Revision. sigma-aldrich.com.

Sipes I.G. and A. J. Gandolfo, 1991. Biotransformation of Toxicants. In Casarett and Doull's Toxicology. Amdur, M.O, Doull, J. And Klasses, C.D., Editors. Pergamon Press. New York. Second Edition (1991).

Snelder D. J., M. D. Masipiqueña and G. R. De Snoo, 2008. Risk assessment of pesticide usage by smallholder farmers in the Cagayan Valley (Philippines). Crop Protection, 27, 747-762.

Spencer E. Y., 1981. Guide to the Chemicals Used in Crop Protection. 7th edition. Publication 1093. Research Branch. Agriculture Canada.

Trimbell J.A., 1991. Principles of Biochemical Toxicology. Pp. 144-147. Taylor and Francis. London. Second Edition.

Uesugi P. Y., 2001. Pesticide outlook, fungal choline biosynthesis, A target for controlling rice blast, pp 26-27.

WHO, 1991. Guidelines to the WHO Recommended Classification of Pesticides by Hazard (IPCS, 39pp.).

Williamson Emily G., 1989. A comparative analysis of the acute toxicity of technical–grade pyrethroid insecticides and their commercials formulations. Ecotoxicol. Environ. Safety 18:27– 34.

Worthing C.R. and S.B. Walker (eds.), 1987. The Pesticide Manual - A World Compendium. 8th ed. Thornton Heath, UK: The British Crop Protection Council.

WSSA, 1983. Herbicide Handbook of the Weed Science Society of America 3rd ed. Champaign, Illinois p. 462-3

Ying G.-G. and B.Williams, 2000. Laboratory study on the interaction between herbicides and sediments in water systems. Environmental Pollution, v.107, p. 399-405.

Zeliger H.I., 2011. Human toxicology of chemical mixtures. In: Toxic Consequences Beyond the Impact of One-component Product and Environmental Exposures. 2nd ed. Elsevier, Oxford.

Zhang C.Z., X.M. Zhang, Z.H. Tian, D.J. He and Liu X.J. 2010. Degradation of Chlorpyrifos and Fipronil in Rice from Farm to Fork and Risk Assessment. Agricultural Sciences in China, Volume 9, Issue 5: 754-763.