MINI-REVIEW

Critical Review on the Carcinogenic Potential of Pesticides Used in Korea

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Abstract

Pesticides used in Korea are grouped by four classes of hazard (extremely, highly, moderately and slightly hazardous) based on acute oral and dermal toxicity in the rat. However, there is little information of carcinogenic effects. The aim of this study was to evaluate potential carcinogenicity for active ingredients of pesticides used in Korea. A total of 1,283 pesticide items were registered under the Pesticide Control Act of which 987 were commercially available. Of these 987 items, 360 active ingredients not duplicated were evaluated for carcinogenicity using the carcinogen list established by the US Environmental Protection Agency (EPA). Some 25 out of 360 ingredients were classified as likely to be carcinogenic (probable) to humans and 52 had suggestive evidence of carcinogenic potential (suspected) based on the US EPA classification. Some 31% of 987 items contained probable or suspected human carcinogenic ingredients. Carcinogenic pesticides accounted for 24% (5,856/24,795 tons) of the total volume of consumption in Korea. Interestingly, pesticides with lower acute toxicity were found to have higher carcinogenic potential. Based on these findings, the study suggests that it is important to provide information on long-term toxicity to farmers, in addition to acute toxicity data.

Keywords: Pesticides - active ingredients - carcinogenicity - MSDS - Korea

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Introduction

Pesticides, including herbicides, insecticides, fungicides and bactericides, have been widely used to control pests and pest-induced diseases in the world (Zhang et al., 2011). In terms of average pesticide use per unit arable and permanent crop area, Korea ranked as the second largest user of pesticides (12.5 kg/ha) among OECD countries in 2003 (OECD, 2008). So, in the aspect of safety and health, pesticide is one of the most important chemicals that should be carefully controlled in Korea.

Employers in chemical manufacturing or importing business should provide the material safety data sheets (MSDS) of the relevant chemical to employees under the Industrial Safety and Health Act. However, pesticides have not been included in the MSDS program as it has been regulated by other registration since 1995 (Ministry of Labor, 1995). From 1957 to 1996, pesticide manufacturers or importers should get permit from the Ministry of Food, Agriculture, Forestry and Fisheries. Since 1997, all pesticides manufactured, imported and consumed are supposed to be registered to the authority of the Korea Rural Development Administration (KRDA) by the Pesticide Control Act in Korea (MFAFF, 2010). Manufacturers, importers, dealers and applicators of pesticides should carefully deal with pesticides according to the Restrictive Handling Criteria of Pesticide (RHCP) noticed by the KRDA(KRDA, 2009).

According to the RHCP, pesticides used in Korea were grouped by four classes of hazard (I; extremely hazardous, II; highly hazardous, III; moderately hazardous, and IV; slightly hazardous) for human and fish toxicity based on acute oral and dermal toxicity to the rat. A growing number of well-designed epidemiological and molecular studies provide substantial evidence that the pesticides used in agricultural, commercial, and home and garden applications are associated with excess cancer risk (Alavanja et al., 2013). However, there is no regulation of hazard communication considering the potential carcinogenic effects of pesticide used in Korea. In this study, the potential carcinogenic pesticides used in Korea were investigated by comparison with the list of Chemicals Evaluated for Carcinogenic Potential (CECP) developed by the Health Effects Division (HED) of the Office of Pesticide Program (OPP) in the US Environmental Protection Agency (EPA).

Chemicals Evaluated for Carcinogenic Potential (CECP)

US EPA reviews studies submitted when a pesticide is proposed for registration. Studies are required in two species (mice and rats) and two sexes (males and females). These studies are required for all pesticides used on food

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and some non-food pesticides that could lead to long-term exposures in humans (US EPA, 2009).

The HED of the OPP performs an independent review of studies conducted in mice and rats to evaluate the carcinogenic potential of pesticides. The results of the independent review are peer-reviewed by the Cancer Assessment Review Committee. This committee recommends a cancer classification. EPA's guidelines for evaluating the potential carcinogenicity of chemicals have been updated over the years to reflect increased understanding of ways chemicals may cause cancer.

EPA issued its first set of principles to guide evaluation of human cancer potential in1976. In 1986, EPA issued updated guidance, which included a letter system (A-E) for designating degree of carcinogenic potential (US EPA, 1986). In the 1986 guidelines, hazard identification and the weight-of-evidence process focused on tumor findings. The human carcinogenic potential of agents was characterized by a six-category alphanumeric classification system (A, B1, B2, C, D, and E).

In 1996, EPA released "Proposed Guidelines for Carcinogen Risk Assessment," which used descriptive phrases rather than the alphanumeric classification to classify carcinogenic potential (US EPA, 1996). In the 1996 classification structure, increased emphasis was placed on discussing characterization of hazard, dose-response, and exposure assessments. The hazard and weight of evidence process embraced an analysis of all relevant biological information and emphasized understanding the agent's mode of action in producing tumors to reduce the uncertainty in describing the likelihood of harm. By 1999, the science related to carcinogens had advanced significantly. EPA issued draft guidelines that continued the greater emphasis on characterization discussions for hazard, dose-response assessment, exposure assessment, risk characterization and the use of mode of action in the assessment of potential carcinogenesis. In addition, the guidelines included consideration of risk to children, as well as addressing other issues such as nuances related to the amount and adequacy of data on a chemical.

In March, 2005, EPA released its final Guidelines for Carcinogen Risk Assessment (US EPA, 2005). These guidelines represent the culmination of a long development process, replacing EPA's original cancer risk assessment guidelines (US EPA, 1986) and its interim final guidelines (US EPA, 1999). In this study, the list of CECP by the OPP through 2006 could be utilized by getting from US EPA via e-mail. It consisted of 400 agrochemicals including 397 with CAS number (Table 1).

Database of Agrochemicals Used in Korea

A total of 1,283 agrochemical items listed on the RHCP in 2009 were entered into the basic database. After excluding items that did not used from 2004 to 2008 by comparison with Agrochemicals Year Book published by Korea Crop Protection Agency in 2009 (KCPA, 2009), 987 items were left. For these 987 items, 360 active ingredients with CAS number were finally selected for evaluation of carcinogenicity using the list of CECP established by the HED of the OPP in the US EPA. All of database for carcinogenicity and active ingredients were entered into Excel spreadsheet and merged by using CAS No. Data analysis was performed by using Microsoft Access 2007.

Comparison between Korean Database of Agrochemicals and CECP

Among 360 ingredients, 25 ingredients (6.9%) were classified as likely to be carcinogenic (probable) to humans and 52 (14.4%) had suggestive evidence of carcinogenic potential (possible) based on the US EPA classification

Table 1. List of Chemicals Evaluated for Carcinogenic Potential by Office of Pesticide Programs in US EPA through 2006

Year	Classification	Number
1986	A - Human carcinogen	0
	B - Probable human carcinogen	28
	C - Possible human carcinogen	66
	D - Not classifiable as to human carcinogenicity	37
	E - Evidence of non-carcinogenicity for humans	67
1996	Known/likely	1
	Cannot be determined	1
	Not likely	3
1999	Carcinogenic to humans	0
	Likely to be carcinogenic to humans	35
	Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential	25
	Data are inadequate for an assessment to human carcinogenic potential	7
	Not likely to be carcinogenic to humans	0
2005	Carcinogenic to humans	0
	Likely to be carcinogenic to humans	6
	Suggestive evidence of carcinogenic potential	8
	Inadequate information to assess carcinogenic potential	1
	Not likely to be carcinogenic to humans	115
Chemicals with CAS number		397
Total		400

Table 2. Summary of Carcinogenicity for Active Ingredients of Pesticide Used in Korea Based on the US EPA Carcinogen List

Classification	Number of active ingredients (%)
A - human carcinogen or Carcinogenic to humans	0 (0.0)
B - Probable human carcinogen or Likely to be carcinogenic to humans	25 (6.9)
C - Possible human carcinogen or Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential or Suggestive evidence of carcinogenic potential	52 (14.4)
D - Not classifiable as to human carcinogenicity or Cannot be determined or Data are inadequate for an assessment to human carcinogenic potential or Inadequate information to assess carcinogenic potential	14 (3.9)
E - Evidence of non-carcinogenicity for humans or Not likely or Not likely to be carcinogenic to humans	83 (23.1)
Not listed	186 (51.7)
Total	360 (100.0)

Table 3. List of Active Ingredients having Carcinogenic Potential for Humans

GHS* classification	US EPA classification	No.	Chemicals
Category 1B - presumed to have carcinogenic potential for humans	Group B2 - probable human carcinogen	9	Chlorothalonil , Cyproconazole, Daminozide, Folpet, Metiram, Procymidone, Propargite, Terrazole, Thiodicarb
	Likely at prolonged, high-level exposures, but not likely at dose levels that do not cause cytotoxicity and regenerative cell hyperplasia	1	Captan
	Likely to be carcinogenic to humans	13	Benthiavalicarb-isopropyl, Butachlor, Carbaryl, Ethoprop, Iprodione, Iprovalicarb, Kresoxim-methyl, Oryzalin, Pyraflufenethyl, Spirodi clofen, Thiacloprid, Thiophanate-methyl, Toly fluanid
	Likely to be carcinogenic to humans (high doses), not likely to be carcinogenic to humans (low doses)	2	Alachlor, Trichlorfon
Category 2 - suspected human carcinogens	Group C - possible human carcinogen	35	Acephate, Benomyl, Bifenthrin, Carbendazim (MBC), Clofentezine, Cypermethrin, Cyperme thrin, Dichlobenil, Dicofol, Difenoconazole, Dimethoate, Ethalfluralin, Ethyl-parathion, Fen buconazole, Fipronil, Hexaconazole, Hexythi azox, Isoxaben, Linuron, Methidathion, Metolachlor, Oadiazon, Oxadixyl, Oxyfluofen, Pendimethalin, Phosphamidon, Prodiamine, Propiconazole, Pyrimethanil, s-Metolachlor, Tebuconazole, Triadimefon, Triadimenol, Trif luralin, Vinclozolin
	Suggestive evidence of carcinogenic potential	3	Amitraz, Dithianon, Metrafenone
	Suggestive evidence of carcinogenicity to humans	2	Fluazinam, Molinate
	Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential	12	Benfluralin, Boscalid, Buprofezin, Chlor fenapyr, Dichlorvos, Flonicamid, Malathion, Mecoprop-P, Penoxulam, Propanil, Tebufen pyrad, Triforine
Total		77	

* GHS : globally harmonized system

Table 4. Table 4. Distribution of Carcinogenic Items by Classification of Pesticides on the Basis of Pest Control

GHS classification*		Classification on the basis of pest control**						Total
		IF	F	I	P	H	O	
Category 1B	N(%)	1(5.3)	75(20.8)	14(4.6)	1(3.2)	17(6.3)	0(0.0)	108(10.9)
Category 2	N(%)	0(0.0)	76(21.1)	62(20.5)	1(3.2)	60(22.1)	0(0.0)	199(20.2)
Not applicable	N(%)	18(94.7)	209(58.1)	226(74.8)	29(93.5)	194(71.6)	4(100)	680(68.9)
Total	N(%)	19(100)	360(100)	302(100)	31(100)	271(100)	4(100)	987(100)

*GHS (globally harmonized system): Category 1B - presumed to have carcinogenic potential for humans, Category 2 - suspected human carcinogens; ** IF (insect-fungicide), F (fungicide), I (insecticide), P (plant growth regulator), H (herbicide), O (others)

Table 5. Comparison of Acute Toxicity and Carcinogenicity for Pesticide Items Used in Korea

GHS classification*		Acute toxicity**			Total
		II	III	IV	
Category 1B	N (%)	0 (0)	6 (0.6)	102 (10.3)	108 (10.9)
	M/T (%)	0 (0)	110 (0.4)	2,828 (11.4)	2,938 (11.8)
Category 2	N (%)	4 (0.4)	32 (3.2)	163 (16.5)	199 (20.2)
	M/T (%)	748 (3.0)	326 (1.3)	1,844 (7.4)	2,918 (11.8)
Not applicable	N (%)	11 (1.1)	91 (9.2)	578 (58.6)	680 (68.9)
	M/T (%)	1,122 (4.5)	5,102 (20.6)	12,715 (51.3)	18,939 (76.4)
Total	N (%)	15 (1.5)	129 (13.1)	843 (85.4)	987 (100)
	M/T (%)	1,870 (7.5)	5,538 (22.3)	17,387 (70.1)	24,795 (100)

* GHS (globally harmonized system): Category 1B - presumed to have carcinogenic potential for humans, Category 2 - suspected human carcinogens; ** Acute toxicity for human; II (highly hazardous), III (moderately hazardous), IV (slightly hazardous)

Table 6. Major Pesticide Items with Probable Human Carcinogenic Potential in Korea

Class*	Item name	Formulation type**	Acute toxicity***	Consumption per year, M/T
H	Butachlor	GR	IV	421.5
F	Chlorothalonil	WP	IV	372
F	Thiophanate-methyl	WP	IV	328
H	Alachlor	GR	IV	261.7
H	Alachlor	EC	IV	222

*Class: H (herbicide), F (fungicide); **Formulation type: GR (granule), WP (wettable powder), EC (emulsifiable concentrate); ***Acute toxicity: IV (slightly hazardous)

(Table 2). On the basis of the globally harmonized system (GHS) of classification of carcinogens (UN, 2011), Category 1B - presumed to have carcinogenic potential for humans or Category 2 - suspected human carcinogens accounted for 21.3% of the total 360 ingredients. The list of 77 active ingredients having carcinogenic potential for humans is given in Table 3.

In terms of items, 31.1% of 987 items contained one or more of the active ingredients classified as the presumed to have carcinogenic potential for humans or suspected human carcinogens (Table 4). Table 4 also shows that the highest proportion of items with carcinogens classified as Category 1B or 2 was 41.9% of fungicides and herbicide, insecticide were followed, respectively 28.4% and 25.1% by the type of pest control.

The results of comparison between acute toxicity and carcinogenicity for pesticide items used in Korea were given in Table 5. Probable (Category 1B) or suspected (Category 2) human carcinogenic pesticides accounted for 23.6% (5,856/24,795 tons) of the total volume of consumption in Korea. After comparing acute toxicity and carcinogenicity, it was found that 10.3% of the total pesticide items had slightly acute toxicity but probable human carcinogenicity. Interestingly, pesticides with lower acute toxicity were found to have higher carcinogenic potential. Among 108 (Category 1B) and 199 (Category 2) pesticides classified as potential carcinogenic items, 94.4% and 81.9% of them showed slightly acute toxicity, respectively.

The most widely used pesticides with probable human carcinogenic potential were butachlor for herbicide and chlorothalonil (fungicide), Thiophanate-methyl (fungicide), alachlor (herbicide) were followed (Table 6). However, all of these have slightly hazardous acute toxicity.

Discussion

There have been a lot of studies to evaluate the association between occupational exposure to pesticide and cancer risk. More recent systematic review studies or case-control studies reported positive association between exposure to pesticides and several cancers including prostate cancer (Van Maele-Fabry and Willems, 2004; Koutros et al., 2010; Doolan G et al., 2014), non-Hodgkin lymphoma (NHL) (Merhi et al., 2007; Balasubramaniam et al., 2013; Yildirim et al., 2013; Schinasi and Leon, 2014), leukemia (Merhi et al., 2007; Van Maele-Fabry et al., 2008), multiple myeloma (Merhi et al., 2007) and lung cancer (Ganesh et al., 2011; Luqman et al., 2014). In the case of esophageal or gastric cancer, no relationship with pesticide usage was reported in recent Turkey study (Yildirim et al., 2014). A large number of studies in Europe and US reported little or no association between pesticides and breast cancer. However, Shakeel et al. (2010) found that the level of pesticide exposure is higher in developing countries than the developed countries. DDT is found to be positively associated with breast cancer risk. They suggested that more studies are needed in the developing and third world countries, investigating the relation between pesticides and breast cancer risk as the sheer amount of pesticides being relentlessly used in these countries due to lack of proper government regulations.

In terms of specific ingredients of pesticides, Schinasi and Leon (2014) systematically reviewed more than 25 years' worth of epidemiologic literature on the relationship between pesticide chemical groups and active ingredients with NHL. This review indicated positive associations between NHL and carbamate insecticides such as carbaryl (meta RR, 95%CI: 1.7, 1.3-2.3), organophosphorus insecticides malathion (meta RR, 95%CI: 1.8, 1.4-2.2), the phenoxy herbicide 2-methyl-4-chlorophenoxyacetic acid (MCPA) (meta RR, 95%CI: 1.5, 0.9-2.5), and an organochlorine insecticide lindane (meta RR, 95%CI: 1.6, 1.2-2.2).

Alavanja et al. (2013) integrated the epidemiological, molecular biology, and toxicological evidence emerging from recent literature assessing the link between specific pesticides and several cancers including prostate cancer, non-Hodgkin lymphoma (NHL), leukemia, multiple myeloma, and breast cancer. They emphasized that, although the review was not exhaustive in its scope or depth, the literature does strongly suggest that the public health problem related to cancer burden among pesticide applicators and others due to pesticide exposure is real.

In this study, the evaluation of the potential carcinogenicity of pesticide used in Korea was performed by comparing with carcinogen list established by US EPA. Probable or suspected human carcinogenic pesticides accounted for 24% (5,856/24,795 tons) of the total volume of consumption in Korea. In particular, pesticides with lower acute toxicity were found to have higher carcinogenic potential. Over 80% of pesticide items classified as probable or suspected carcinogens had slightly acute toxicity. Based on these findings, the study suggests that it is important to provide the information of long-term toxicity, in addition to acute toxicity data.

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