

## Comparative Estimation of Exposure Level and Health Risk Assessment of Highly Produced Pesticides to Agriculture Operators by Using Default Dermal Absorption Rate or Actual Measurement Values

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Pesticides are widely used to prevent loss of agricultural production but extensive exposure can induce health problems to pesticide operators. This study was performed to evaluate the health risk of highly produced pesticides used in fruit growing farm land by comparison of estimated exposure level with AOEL using KO-POEM program. AOEL was driven based on NOAEL of each pesticide evaluated by JMPR, EFSA or KRDA. In calculation of exposure level, types of formulation, dilution factors, spraying duration and motor type and exposure protection device were allocated according to actual condition of use. Dermal absorption rate was differently applied among EFSA default values (25% or 75%), general default value (10%) or real test result values to know the plausibility of default values and safety of pesticide to operators in outline. Twenty pesticide ingredients (fungicides and insecticides) were produced more than 30 tons per year, which were mancozeb, chlorothalonil, imidacloprid and etc in order. Dermal absorption rates obtained from studies were various from 0.07 to 81% but mostly under 10%. The estimated exposure levels showed big differences more than 10 times higher when using EFSA default rate and up to 5 times higher when using general rate of 10% comparing using rates of test results. Mancozeb, chlorthalonil, diazinon and chlorpyrifos presented still higher exposure level than AOEL even when using test absorption rate from study, which suggests that re-evaluation of AOEL or dermal exposure absorption rate or strict management are required for health protection of operators who use those four pesticides in farm land.

**Key Words:** Pesticide operator, Risk assessment, AOEL, Dermal absorption rate, Estimated exposure level

### INTRODUCTION

Pesticides are widely used to control harmful insects and to prevent loss of agricultural production. However, high exposure can induce health problems including neurotoxicity, hepatotoxicity and etc. to pesticide operators (Choi and Kim, 2014). Therefore, Acceptable Operator Exposure Level (AOEL) is established during authorization of pesticides to

prevent the exposure level does not exceed operators' health protection level, AOEL (You et al., 2014).

Field workers get a majority of internal dose through dermal contact to pesticides and most pesticides have low to moderate vapor pressure. It was reported that more than 90% of total exposure is come from the skin contact during application of agrochemicals (Finley et al., 1994; kim et al., 2012). In calculation of exposure level of pesticide to operators, dermal absorption rate, dilution factor, kind of solvent,

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spraying duration, spraying motor type and exposure protection device are all key factors for precise estimation (Ueda et al., 2009). Among them, dermal absorption rate is the most important factor for calculation of internal dose of pesticide because internal dose is dependent on penetration efficacy through skin barrier (Poet, 2000).

UK-POEM or KO-POEM were kinds of developed models to measure exposure level of pesticide to operators. When measuring exposure level of pesticide to operator by using the models, dermal absorption rate should be presented for each pesticide product. However, information of dermal absorption rate was limited. EFSA recommended default dermal absorption rate 75% when the concentration of active ingredient in a product is lower than 5% and 25% when active ingredient is higher than 5% (EFSA, 2012). Also, default dermal absorption rate 10% was also suggested by EFSA (2012) for chemicals with a molecular weight higher than 500 and log Kow value smaller than -1 or higher than 4.

This study was performed to evaluate the health risk of highly produced pesticides used in fruit growing farmland by comparison of estimated exposure level with AOEL. The exposure level was driven by using three kinds of different dermal absorption rates, which were EFSA default values (25% or 75%), general default value (10%) or actual measurement values coming from study to know the safety of pesticide to operators' health and the plausibility of default dermal absorption rates in estimation of exposure level.

## MATERIALS AND METHODS

### Selection of pesticides and information survey

To select highly produced pesticides (more than 30 tons/year), information of annual production amount of pesticide and methods of pesticides using in field were obtained through the annual report of pesticide crop protection guideline (Korea Crop Protection Association, 2015).

### AOEL evaluations

Information of point of departure values of toxicity (NOAEL) and AOEL were obtained through JMPR, EFSA and Korea RDA.

### Estimation of exposure level

KO-POEM program was used to drive pesticide exposure level to operators. Parameters including working time, work rate, method of spraying and personal protection device used for the calculation of exposure amount of pesticide to operators were presented in Table 3. The exposure level of highly produced pesticides to operators were calculated by using EFSA default dermal absorption rate values (25% or 75%), typically used default values (10%) and actual absorption rate obtained from studies. Related to this scheme of application of dermal absorption rate was shown in Fig. 1.

### Risk assessment for pesticide operators

For pesticide operator health risk assessment, the ratio of estimated exposure level driven from KO-POEM per AOEL (Toxic Exposure Ratio, TER) was calculated. Risk assess-

**Table 1.** Highly produced pesticides (more than 30 tons/year) in 2015 in KOREA

Ingredient	Annual Output (tons/year)	Category
Mancozeb	1,640	Fungicide
Chlorothalonil	443	Fungicide
Imidacloprid	355	Insecticide
Propineb	243	Fungicide
Thiophanate-methyl	208	Fungicide
Dithianon	93	Fungicide
Myclobutanil	64	Fungicide
Diazinon	63	Insecticide
Acibenzolar-S-methyl	55	Fungicide
Acephate	52	Insecticide
Iprodione	49	Fungicide
Fluazinam	49	Fungicide
Metalaxyl	49	Fungicide
Captan	47	Fungicide
Copper oxychloride	44	Fungicide
Kasugamycin	44	Fungicide
Cypermethrin	43	Insecticide
Copper hydroxide	38	Fungicide
Chlorpyrifos	34	Insecticide
Tebuconazole	34	Fungicide

ment for pesticide operator was based on TER. It was judged to be hazard if TER exceed 1 and to be safe when TER equal to or below 1.

## RESULTS

### Highly produced pesticides and their use in farmland

20 pesticides were produced more than 30 tons per year in 2015 in KOREA among fungicides and insecticides used in fruit growing farmland (Korea Crop Protection Association 2015) Mancozeb (1,640 tons), chlorothalonil (443 tons),

imidacloprid (355 tons), propineb (243 tons) and thiophanate-methyl (208 tons) and etc were found highly produced pesticides in order (Table 1).

### AOEL of highly produced pesticides

Point of departure values of toxicity (NOAEL) and AOEL were obtained through JMPR, EFSA and Korea RDA (Table 2). For 20 kinds of highly produced pesticides, AOELs were ranged from 0.0002 to 0.19 mg/kg bw/day. The endpoint toxicities were found in mainly 90 days repeat oral toxicity studies in rats or dogs and toxicities including thyroid gland

**Table 2.** Toxicity values (NOAEL), AOEL and dermal absorption rate of highly produced pesticides

Ingredient	Toxicity (NOAEL, mg/kg bw/day)	AOEL (mg/kg bw/day)	Dermal absorption rate from actual test
Mancozeb	Rat 90days repeat/oral: Inhibition of thyroid peroxidase, thyroid hyperplasia (7)	0.035 <sup>a)</sup>	C : 1%, D : 4% <sup>d)</sup>
Chlorothalonil	Rat 1year repeat/oral: Tumor pre-symptom in kidney and stomach (2.7)	0.009 <sup>a)</sup>	D : 10% <sup>e)</sup>
Imidacloprid	Rabbit teratology toxicity: Decrease of maternal body weight and feed intake (8)	0.08 <sup>a)</sup>	C : 7.9%, D : 11.4% <sup>d)</sup>
Propineb	Rat 90days repeat/oral: Muscle atrophy (7.6)	0.046 <sup>a)</sup>	–
Thiophanate-methyl	Dog 1year repeat/oral: Increased liver weight, anemia (8)	0.08 <sup>a)</sup>	–
Dithianon	Dog 90days repeat/oral: Liver, kidney toxicity (3)	0.014 <sup>a)</sup>	C : 0.07%, D : 0.79% <sup>g)</sup>
Myclobutanil	Dog 1year repeat/oral: Increased liver weight, hepatomegaly (3.09)	0.031 <sup>a)</sup>	D : 25% <sup>h)</sup>
Diazinon	Dog 90days repeat/oral: Cholinesterase inhibition (0.02)	0.0002 <sup>a)</sup>	D : 14.1% <sup>i)</sup>
Acibenzolar-S-methyl	Dog 90day sub-acute toxicity: Haemolytic anaemia (10)	0.03 <sup>b)</sup>	C : 16%, D:81% <sup>j)</sup>
Acephate	Rat 90days repeat/oral: Cholinesterase inhibition (0.58)	0.0058 <sup>a)</sup>	–
Iprodione	Rat 90days repeat/oral: Changed weight of liver and adrenal gland (31)	0.19 <sup>a)</sup>	D : 0.65% <sup>k)</sup>
Fluazinam	Rabbit teratology toxicity: Delayed ossification (1)	0.0035 <sup>a)</sup>	–
Metalaxyl	Dog 90days repeat/oral: Liver toxicity, anemia (8)	0.08 <sup>a)</sup>	–
Captan	Rabbit teratology study: Teratogenesis of fetus (10)	0.1 <sup>c)</sup>	D : 0.9% <sup>l)</sup>
Copper oxychloride	Human: Non toxic (0.2)	0.072 <sup>a)</sup>	–
Kasugamycin	Rabbit teratology study: Decreased weight, abortion (10)	0.01 <sup>a)</sup>	–
Cypermethrin	Dog 90days repeat/oral: Disordered nervous system (12.5)	0.063 <sup>a)</sup>	D : 25% <sup>m)</sup>
Copper hydroxide	Human: Non toxic (0.2)	0.072 <sup>a)</sup>	–
Chlorpyrifos	Rat comparative cholinesterase assay repeat/oral: Cholinesterase inhibition (0.1)	0.001 <sup>a)</sup>	D : 1% <sup>n)</sup>
Tebuconazole	Dog 1year repeat/oral: Adrenal zona fasciculata cell hypertrophy (3)	0.03 <sup>a)</sup>	–

C: Original product formulation, D: Diluted product for spraying, –: No data provided

<sup>a)</sup>National Institute of Agricultural Science KOREA (2016), <sup>b)</sup>European Commission (2002), <sup>c)</sup>European Commission (2008), <sup>d)</sup>INCHEM, mancozeb database, <sup>e)</sup>California Environment Protection Agency (2005), <sup>f)</sup>Li et al (2012), <sup>g)</sup>CTGB (2016), <sup>h)</sup>California Department of Food and Agriculture Worker Health and Safety Branch (1988), <sup>i)</sup>NPIC database, <sup>j)</sup>European Commission (2002), <sup>k)</sup>EPA (1995), <sup>l)</sup>EPA (1997), <sup>m)</sup>EPA (1996), <sup>n)</sup>European Commission (2005)

**Table 3.** Condition of pesticide use including working time, work rate and method of spraying for the calculation of exposure level of pesticide to operators

Pesticide formulation	Wearable device for protection		1 day spraying area (Work rate/day)	1 day spraying time
	During mix/loading	Spraying application		
	Speed sprayer	Speed sprayer	Speed sprayer	
Water dispersible granule	Glove and mask (FFP3)	Glove	2 ha	6 hr
Wattable powder	Glove and mask (FFP3)	Glove	2 ha	6 hr
Emulsifiable concentrate	Glove	Glove	2 ha	6 hr
Liquid Formulation	Glove	Glove	2 ha	6 hr

hyperplasia in rats, increased liver weight in dogs, cholinesterase inhibition in rats, delayed ossification in rabbits and etc (Table 2). The lowest AOEL among those of 20 pesticides was 0.0002 mg/kg bw/day for diazinon and the endpoint toxicity was cholinesterase inhibition in dogs treated orally for 90 days with NOAEL 0.02 mg/kg bw/day.

In case for propineb, thiopante-methyl, acepate, fluazinam, metalaxyl, copper oxychloride, kasugamycin, copper hydroxide and tebuconazol, there were no information of dermal absorption rate. Other pesticides have information of dermal absorption rate for concentrated formula or diluted solution used for spraying. The absorption rate was from 0.07% to 81% (Table 2). When dermal absorption rates were provided both for concentrated and diluted products such as mancozeb, imidacloprid, dithianon and acibenzolar-S-methyl, that of diluted solution was higher than concentrated formula of same product ranged from 1.4 to 10 times.

### Estimation of exposure level

In calculation of the exposure level using the KO-POEM program, pesticide formulation type, protective equipment, application method, work rate/day, dose, application volume, duration of spraying was inputted according to the actual condition of use as presented in Table 3.

The estimated exposure level calculated were the highest when using EFSA default dermal absorption values (25% or 75%) and the lowest when using actual measurement values and the differences were mostly 10 times higher in case using EFSA default values. This means the EFSA approach of using default dermal absorption rate is too conservative

in estimation of operator exposure level of pesticides.

The estimated exposure level was similar or a little higher when using 10% default values comparing when using actual measurement values. This results showed that 10% default dermal absorption rate used by KRDA may be appropriate for exposure assessment of pesticide products with limited information. Aggarwal et al. (2015) presented that 6% for liquid and 2% for solid concentrates, irrespective of active substance loading, were appropriate as for default values of dermal absorption rate when no information was available.

### Risk assessment for pesticide operators

When using estimated exposure level derived from EFSA default dermal absorption rate, 35 kinds of products among 41 products showed TER higher than 1. Diazinon wetttable powder had TER 1350. Still 24 pesticide products have TER higher than 1 when using default dermal absorption rate 10%. Among 22 pesticide products which have actual measurement values of dermal adsorption rates from *in vitro* or *in vivo* studies, 9 products showed TER higher than 1, which products are mancozeb (WP), chlorothalonil (WP, FL, WG), some products of dithianon (WP), diazinon (WP) and chlorpyrifos (WP, FL, EC) (Table 4).

Among pesticide products which information of dermal absorption rate were not available, propioneb (WP), acepate (WP), fluazinam (WP, FL, WG), several products of copper oxychloride (WP) and kasugamycin (FL, WG), copper hydroxide (WP) and tebuconazole (WP, EC) presented TER higher than 1 when using estimated exposure level of default dermal absorption rate 10%.

**Table 4.** Ratio of estimated exposure level/AOEL of pesticides which dermal absorption rate coming from EFSA default values, general default values and actual measurement values from study under speed sprayer condition

Ingredient	AOEL (mg/kg bw/ day)	Formula	Estimated Exposure level (TER <sup>a</sup> )		
			EFSA default rates	General default rates	Actual measurement values
Mancozeb	0.035	WP	0.60~1.62 (17.28~46.29)	0.07~0.23 (2.1~6.6)	0.03~0.10 (0.92~2.87)
Chlorothalonil	0.009	WP	0.29~1.62 (32.40~180.01)	0.04~0.23 (4.62~25.66)	0.03~0.24 (3.49~26.17)
		FL	0.22~0.57 (24.00~63.60)	0.03~0.08 (3.42~9.07)	0.03~0.08 (3.49~9.25)
		WG	0.57 (63.88)	0.08 (8.90)	0.08 (8.98)
Imidacloprid	0.08	WP	0.02~0.05 (0.22~0.68)	0.00~0.01 (0.05~0.10)	0.00~0.01 (0.05~0.11)
		WG	0.05 (0.65)	0.01 (0.09)	0.01 (0.10)
		FL	0.03~0.05 (0.03~0.61)	0.00~0.01 (0.05~0.09)	0.01 (0.09)
		LF	0.01 (0.08)	0.05 (0.59)	0.01 (0.09)
Propineb	0.046	WP	1.51 (32.87)	0.22 (4.69)	–
Thiophanate-methyl	0.08	WP	0.08~0.76 (0.95~9.45)	0.01~0.11 (0.13~1.35)	–
		FL	0.22~0.54 (2.70~6.71)	0.03~0.07 (0.39~0.94)	–
Dithianon	0.014	WP	0.14~0.81 (10.03~57.86)	0.02~0.12 (1.43~8.25)	0.00~0.02 (0.20~1.13)
		FL	0.22~0.46 (15.43~23.14)	0.03~0.07 (2.20~4.73)	0.00~0.01 (0.30~0.65)
		WG	0.32~0.71 (3.21~7.06)	0.04~0.10 (23.01~50.63)	0.01 (0.39~0.85)
Myclobutanil	0.031	WP	0.04~0.06 (1.45~2.16)	0.01 (0.21~0.37)	0.02 (0.51~0.74)
Diazinon	0.0002	WP	0.27 (1350.05)	0.04 (192.48)	0.05 (269.08)
Acibenzolar-S-methyl	0.03	WP	0.01 (0.36)	0.00 (0.05)	0.01 (0.39)
		FL	0.02 (0.51~0.64)	0.00 (0.07~0.09)	0.02 (0.54~0.68)
Acephate	0.0058	WP	0.22 (37.24)	0.03 (5.31)	–
Iprodione	0.19	WP	0.27~0.54 (0.20~0.41)	0.04~0.08 (1.42~2.84)	0.01 (0.03~0.04)
		FL	0.46 (2.44)	0.07 (0.35)	0.01 (0.05)
Fluazinam	0.0035	WP	0.17~0.27 (49.37~77.15)	0.02~0.04 (7.04~11.00)	–
		FL	0.16~0.27 (44.74~77.15)	0.02~0.04 (6.38~11.00)	–
		WG	0.27 (76.71)	0.04 (10.69)	–
Metalaxyl	0.08	WP	0.16 (2.03)	0.02 (0.29)	–
Captan	0.1	WP	1.08~1.30 (10.80~12.96)	0.15~0.18 (1.54~1.85)	0.03 (0.28~0.33)
		WG	0.54 (5.37)	0.07 (0.75)	0.01 (0.11)
Copper oxychloride	0.072	WP	0.25~0.91 (3.47~12.60)	0.04~0.13 (0.49~1.80)	–
Kasugamycin	0.01	WP	0.04~0.06 (3.73~6.21)	0.01 (0.53~0.89)	–
		FL	0.08~0.11 (4.36~8.05)	0.01 (0.62~1.12)	–
		WG	0.04~0.05 (10.74)	0.01 (1.50)	–
Cypermethrin	0.063	EC	0.06 (0.91)	0.01 (0.14)	0.02 (0.35)
Copper hydroxide	0.072	WP	0.54~0.83 (7.50~11.55)	0.08~0.12 (1.07~1.65)	–
		WG	0.50 (6.92)	0.07 (0.96)	–
Chlorpyrifos	0.001	WP	0.16~0.34 (162.01~337.51)	0.02~0.05 (23.10~48.12)	0.00~0.01 (4.39~9.14)
		FL	0.16 (162.01)	0.02 (23.10)	0.00~0.02 (4.39~22.68)
		EC	0.11~0.47 (114.50~465.15)	0.02~0.07 (28.80~68.04)	0.01~0.02 (9.42~22.68)
Tebuconazole	0.03	WP	0.08~0.25 (2.70~8.28)	0.01~0.04 (0.38~1.18)	–
		EC	0.15~0.20 (5.08~6.57)	0.03 (0.86~1.07)	–
		FL	0.04~0.18 (1.44~6.00)	0.01~0.03 (0.21~0.86)	–
		WG	0.13 (4.47)	0.02 (0.62)	–

WP: Wettable powder, FL: Flowable, WG: Water-dispersible granule, LF: Liquid formulation, EC: Emulsifiable concentrate, -: No data provided

a) TER (Toxic exposure ratio) = Estimated exposure level/AOEL, estimated exposure level was driven by application of EFSA default dermal absorption rate (25% or 75%) or general default rate (10%) or actual dermal absorption rate coming from *in vitro* or *in vivo* study

Actual measurement value of dermal absorption rate is very important for estimation of accurate exposure level.

This study showed the exposure level is directly dependent on dermal absorption rate and EFSA approach using default

dermal absorption rate 25% or 75% is too conservative and does not reflect actual situation comparing general dermal absorption rate 10%.

## DISCUSSION

Pesticides are widely used to prevent the loss of agricultural production, but they can cause health problems to pesticide operators. Therefore, operator's health risk assessment of highly produced pesticides used in farm land is required.

Operator's health risk assessment is performed by the comparison of estimated exposure level with AOEL if TER is higher than 1, it is concerned level for operator's health.

In Korea, after reviewing all toxicological data such as

acute toxicity, short-term toxicity, chronic toxicity, carcinogenicity, reproductive toxicity, teratogenicity and genotoxicity, AOEL is decided. In many cases, AOEL was set based on NOAEL of 90 days or short-term toxicity and by considering uncertainties of interspecies and individual differences and data gaps of studies (Damalas and Eleftherohorinos, 2011; Hong et al., 2007, 2010; You et al., 2014). In addition, the oral absorption rate was used as a correction factor to convert the external dose to the internal dose when oral absorption rate was less than 80% (You et al., 2014).

Dermal absorption rate is one of key factors for estimation of exposure level of pesticides to operators (Ueda et al., 2009). Exposure level of highly produced pesticides to operators was calculated by using EFSA default dermal absorption rate values (10%, 25% or 75%), typical default

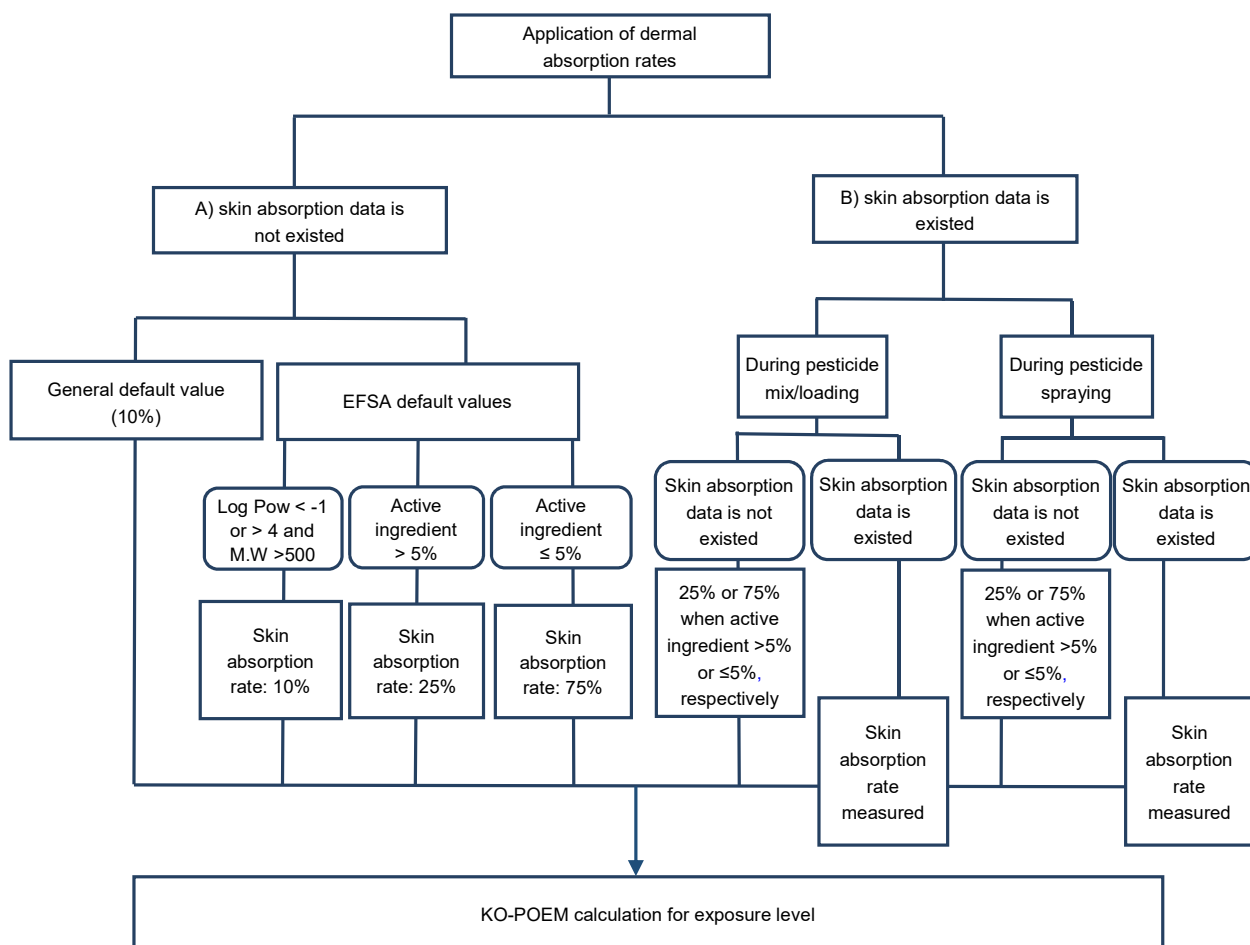


Fig. 1. Scheme of application of dermal absorption rate for estimation of exposure level.

value (10%) or actual measurement rate obtained from studies and then compared the estimated levels with each other. 25% dermal absorption rate was allocated when active substance content is higher than 5% and 75% dermal absorption rate was used when active substance content is equal to or lower than 5% according to EFSA recommendation. Default 10% dermal absorption rate was also used because it is accepted and used by KRDA but EFSA accept the value when a chemical having  $\log Pow < -4$  or  $> 1$  and molecular weight  $> 500$ . Related to this scheme of application of dermal absorption rate was shown in Fig. 1.

Aggarwal et al. (2015) reported that absorption does not increase linearly beyond a 5-fold increase in dilution comparing concentrated one and as for default dermal absorption rate 30% was proposed for all spray dilution. In our investigation the dermal absorption rate of diluted spray was lower than 30% except acibenzolar-S-methyl. EU recommends default absorption rate 75% when the concentration of ingredient is lower than 5%, which value was found too conservative considering actual measurement values.

Actual measurement value of dermal absorption rate is very important for estimation of accurate exposure level. The estimated exposure level was similar or a little higher when using 10% default values comparing when using actual measurement values. This results showed that 10% default dermal absorption rate used by KRDA may be appropriate for exposure assessment of pesticide products with limited information.

The degree of pesticide hazard by dermal absorption is related with the toxicity potency of pesticide, duration of the exposure, pesticide formulation, spraying types and the absorption rate (Dosemeci et al., 2001).

In our study diazinon presented too high exposure level comparing AOEL of 0.0002 mg/kg bw/day. Chlorothalonil and chlorpyrifos also showed risk concern for operators when they use any kinds of formula of the pesticides even when estimate exposure level using actual measurement values. And also propineb, acepate and fluzinam need information of actual dermal absorption rate by study for higher TER by using 10% default dermal absorption rate.

In conclusion, this study presented outlined health risk of highly produced pesticides used in fruit growing farmland

when operators are exposed to the pesticides during loading and spraying and proposed that re-evaluation or study of dermal absorption rate are required for diazinon, chlorothalonil, chlorpyrifos, propineb, acepate and fluzinam because the estimated exposure levels are calculated higher than AOEL and the amount of use are high in agriculture area.

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### Abbreviations

AOEL: Acceptable Operator Exposure Level; KO-POEM: Korea Predictive Operator Exposure Model; NOAEL: NO-Observed-Adverse-Effect-Level; JMPR: FAO/WHO Joint Meeting of Pesticide Residue; EFSA: European Food Safety Agency; KRDA: Korea Rural Development Administration

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### Conflict of interest

The authors declare that they have no competing interests.

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