Food and Chemical Toxicology 123 (2019) 511–519

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Chemical-specific maximum allowable levels for pesticide residues in dietary supplements

Rebecca E. Adams*, Julie A. Brickel[1], Virunya S. Bhat

NSF International, 789 N. Dixboro Rd, Ann Arbor, MI, 48105, USA

ARTICLE INFO

Keywords:
Risk assessment
Pesticide residue
Pesticide tolerance
Pesticide contaminant
Dietary supplement
Botanical ingredient

ABSTRACT

Dietary supplements are regulated by the U.S. FDA as a subset of foods. Most botanical dietary ingredients do not have pesticide tolerances, resulting in the enforcement of zero tolerance or general maximum residue limits (GMRL), rather than utilizing science-informed tolerances. In the current study, chemical-specific maximum allowable levels (MALs) were derived for 185 pesticides by converting existing, authoritative-body human health effects criteria. MALs were derived for 96% of pesticides using criteria established by the U.S. EPA. If multiple authoritative-bodies had established human health effects criteria, the most scientifically-defensible criteria was selected, taking into consideration both carcinogenic and non-carcinogenic endpoints. Five pesticides (o-phenylphenol, pirimicarb, oxadixyl, tetradifon, o,p'-DDT), lacking criteria established by the U.S. EPA had criteria established by other authoritative-bodies that were utilized in the derivation of MALs. Two pesticides did not have any established human health effects criteria (o,p'-DDD and o,p'-DDE). In total, MALs were derived from existing criteria for over 98% of the pesticides in the present study. Consequently, it is demonstrated that human health effects criteria derived by authoritative-bodies can be effectively utilized to derive chemical-specific, science-informed MALs applicable to all food commodities, including botanical ingredients, thereby, minimizing reliance on precautionary zero tolerance and GMRLs.

1. Introduction

1.1. United States (U.S.) dietary supplements industry

In the early 1940s, the first multivitamin tablet was introduced to U.S. markets (NIH, 2007). Since then, growth in dietary supplement use has accelerated rapidly with 76% of U.S. adults, or more than 170 million people, consuming dietary supplements each year (CRN, 2017). According to a 2016 Consumer Survey on Dietary Supplements, general population growth, along with an increase in usage among younger adults, has contributed to the increase in dietary supplement consumption with the industry's overall U.S. economic impact valued at more than $120 billion or 0.68 percent GDP in 2016 (CRN, 2016; Dunham, 2016; Low et al., 2017). Importantly, botanical dietary supplements form a large segment of this market with reports of 61 million people taking herbals/botanicals (Low et al., 2017; CRN, 2016).

1.2. Current U.S. regulations

In the U.S., dietary supplements are regulated by the U.S. Food and

Abbreviations: ADI, Acceptable Daily Intake; APVMA, Australian Pesticides and Veterinary Medicines Authority; BMDL, Benchmark Dose Level; CAS, Chemical Abstracts Service; DSHEA, Dietary Supplement Health and Education Act; EC, European Commission; EFSA, European Food Safety Authority; EMA, European Medicines Agency; EU, European Union; FAO, Food and Agriculture Organization; FFDCA, Federal Food Drug and Cosmetic Act; FQPA, Food Quality Protection Act; GAP, good agriculture practices; GMP, good manufacturing practice; GMRL, general maximum residue limit; IRIS, Integrated Risk Information System; JECFA, Joint FAO/WHO Expert Committee on Food Additives; JMPR, Joint FAO/WHO Meeting on Pesticide Residues; LOAEL, Lowest Observed Adverse Effect Level; MAL, maximum allowable level; MRL, maximum residue limit; NOAEL, No Observed Adverse Effect Level; NOP, National Organic Program; NPS, nonpoint-source; OSF, Oral Slope Factor; PAD, Population Adjusted Dose; PMRA, Pest Management Regulatory Agency; POD, Point-of-Departure; PTDI, provisional Tolerable Daily Intake; RfD, Reference Dose; RSC, Relative Source Contribution; SCCS, Scientific Committee on Consumer Safety; TDI, Tolerable Daily Intake; TTC, Threshold of Toxicological Concern; UF, uncertainty factor; US. EPA, U.S. Environmental Protection Agency; U.S., United States; USDA, United States Department of Agriculture; U.S. EPA, U.S. Environmental Protection Agency; U.S. FDA, U.S. Food and Drug Administration; USP, U.S. Pharmacopeia; USP-NF, USP-New Formulary; WHO, World Health Organization

* Corresponding author.
E-mail addresses: radams@nsf.org (R.E. Adams), jabrickel@Burdockgroup.com (J.A. Brickel), bhat@nsf.org (V.S. Bhat).
[1] Present address: Burdock Group, 859 Outer Rd, Orlando, FL, 32814, USA.

https://doi.org/10.1016/j.fct.2018.11.045
Received 11 October 2018; Received in revised form 16 November 2018; Accepted 19 November 2018
Available online 20 November 2018
0278-6915/

Drug Administration (U.S. FDA) as a subset of foods under the Dietary Supplement Health and Education Act (DSHEA) of 1994 (DSHEA, 1994). Dietary supplements containing botanical dietary ingredients have concentration-based pesticide tolerances established by the U.S. Environmental Protection Agency (U.S. EPA) or, in some cases, by the U.S. FDA. Per the enforcement criteria, the pesticide tolerances in dietary supplements containing botanical dietary ingredients are set to the same levels as foods (DSHEA, 1994; U.S. FDA. CPG Sec. 575.100).

Tolerances for pesticides are governed by the Federal Food, Drug and Cosmetic Act (FFDCA) of 1938 (FFDCA, 1938a). The FFDCA authorizes the U.S. EPA to establish a tolerance for the maximum amount or concentration of a pesticide residue that may be legally present in or on a treated raw agricultural commodity or issue an exemption for a pesticide from the requirement of a tolerance (U.S. FDA. CPG Sec. 575.100). Currently, the U.S. EPA establishes pesticide tolerances as part of the food safety equation ensuring that pesticides can be used with "reasonable certainty of no harm" (U.S. EPA, 2017a). A pesticide tolerance, or maximum residue limit (MRL), is the concentration of a pesticide residue allowed to remain in or on each treated food commodity (U.S. EPA, 2017a). Consequently, current regulations rely on pesticide tolerances specific to each crop, with food consumption data as a driver for which crops are evaluated. Because tolerances and action levels have primarily been established by the U.S. EPA for high-value crops (e.g. grain, fruits, vegetables, etc.); many plant species do not have established pesticide tolerances or action levels (40 CFR Part 180).

The U.S. FDA is responsible for the enforcement of pesticide tolerances and food additive regulations established by the U.S. EPA (FFDCA, 1938b; U.S. FDA. CPG Sec. 575.100). Under FFDCA Sec. 408, a raw agricultural commodity or a processed food or feed is deemed to be adulterated and subject to the U.S. FDA enforcement action if it contains either: 1) a pesticide residue at a level greater than that specified by a tolerance or food additive regulation, or, 2) a pesticide residue for which there is no tolerance, tolerance exemption or food additive regulation (FFDCA, 1938b; U.S. FDA. CPG Sec 575.100). An important tolerance exemption to enforcement includes "unavoidable pesticide residues" (U.S. FDA. CPG Sec 575.100). If a food or feed contains pesticide residues from sources of contamination that cannot be avoided by good agriculture practices (GAPs) or good manufacturing practices (GMPs), the U.S. FDA may establish an action level for such unavoidable pesticide residues (U.S. FDA. CPG Sec. 575.100). An action level specifies the level below which the U.S. FDA exercises its discretion not to take enforcement action and is based on a recommendation from the U.S. EPA (21 CFR Parts 109 and 509; U.S. FDA. CPG Sec. 575.100).

1.3. Zero tolerance

In the absence of an established tolerance or action level (or approved exemption), the pesticide allowance on, or in, food is defined in 40 CFR Part 180.5 as "zero tolerance," which is recognized to be any level below the limit of detection using an applicable analytical method (40 CFR Part 180.5; 40 CFR 180.101(c)). Further, with the advancement of analytical instrumentation, the detection limits for pesticides of interest have been reduced. Consequently, lower concentrations of pesticide residues can be detected on or in products which results in a greater frequency of pesticide residue detections that are subject to the precautionary zero tolerance. As there is currently no comprehensive list for pesticide tolerances and/or action levels for common botanical dietary ingredients in dietary supplements, there has been no option but to enforce the zero tolerance regulation for these materials.

1.4. Nonpoint-source (NPS) pesticide contamination

Pesticides have been used for many years to kill agricultural pests. Consequently, nonpoint-source (NPS) pesticide contamination is of concern when evaluating pesticide tolerances. As a result of NPS pesticide contamination, chemicals can enter and contaminant water and food sources through direct application, runoff, and atmospheric deposition (U.S. EPA, 2005a). In response to NPS pesticide contamination, the U.S. FDA has set action levels for discontinued historical pesticide chemicals that persist in the environment; however, these action levels were established only for non-botanical specified crops or commodities (USP, 2016). Therefore, unlike crops and commodities, botanicals that are subject to unavoidable NPS pesticide contamination continue to be held to the zero tolerance regulation (40 CFR 180.5).

1.5. Pesticide regulations in Canada and the European Union (EU)

The Canadian Food and Drugs Act and Regulations authorizes the Pest Management Regulatory Agency (PMRA) to establish concentration-based MRLs for pesticide-crop combinations (Health Canada, 2015). However, in contrast to the zero tolerance approach utilized in the U.S., when an MRL has not been established for specific pesticide-crop combinations, the PMRA applies a General MRL (GMRL) of 0.1 ppm (Health Canada, 2017; USP, 2016). Similarly, in the EU, concentration-based MRLs are set by the European Commission (EC) for all food and animal feed after the European Food Safety Authority (EFSA) verifies that the residue is safe for all European consumer groups (EC, 2008; EC, 2017). The regulation covers pesticides currently or formerly used in agriculture in or outside the EU (EC, 2008; EC, 2017). Comparable to the regulations established in Canada, a GMRL is applied when a pesticide-crop combination has not specifically been evaluated (EC, 2008; EC, 2017); however, the GMRL established by the EU of 0.01 ppm is 10-fold more conservative than the GMRL established by Canada (0.1 ppm) (EC, 2008; EC, 2017; Health Canada, 2017; USP, 2016).

1.6. Maximum allowable levels (MALs)

The MALs derived for pesticides residues within this analysis are specific to dietary supplements. Thus, the MAL is the estimated daily exposure level at which a chemical in dietary supplements is likely to be without an appreciable risk of adverse effects over an individual's lifetime. Due to the lack of pesticide tolerances and action levels and the subsequent enforcement of zero tolerance by the U.S. FDA on botanical dietary ingredients typically found in dietary supplements, a critical need to establish scientifically-defensible MALs based on chemical-specific human health effects criteria was recognized. The purpose of the present study was to utilize publicly available human health effects criteria derived by international authoritative-bodies to develop chemical-specific, evidence-driven MALs for pesticide residues in dietary supplements, regardless of the food commodity on/in which they are detected, to minimize reliance on precautionary zero tolerance while being mindful of human health risk.

2. Methods

2.1. Study sample

The United States Department of Agriculture (USDA) Prohibited Pesticides List for National Organic Program (NOP) Residue Testing (2011), which contains 185 pesticides that can reliably be identified analytically, was used for the study sample. The NOP and USDA Agricultural Marketing Service established the list of "target" analytes by examining all pesticides, metabolites and environmental contaminants that have been detected and analyzed in the USDA Pesticide Data Program (USDA NOP, 2012). Chemical-specific exposure-based MALs were derived for the unique "target" analytes identified on this list.

2.2. Human health safety assessment

Acceptable or tolerable daily exposures, likely to be without

deleterious human health effects over the lifetime of an individual, are commonly established for a variety of chemicals, including pesticides. These science-informed criteria are derived by utilizing human exposure data when available, but are more frequently derived from toxicological studies in laboratory animals. A No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL), or Benchmark Dose Level (BMDL) is identified in repeat-dose animal toxicity studies as the Point-of-Departure (POD) and then uncertainty factors (UF) are applied to derive an Acceptable Daily Intake (ADI), oral Reference Dose (RfD), or Tolerable Daily Intake (TDI) expressed in mg/kg-day. The total UF applied to the POD is based on the robustness of the chemical-specific dataset; however, for food-use pesticide evaluations, a default UF of 100x is commonly applied to account for interspecies (animal-to-human) and intraspecies (human-to-human) variability (Faustman and Omenn, 2013) (Equation (1)). To characterize the risk of a chemical consumed from the diet, a Population Adjusted Dose (PAD) may be derived utilizing the oral RfD and an additional safety factor (up to 10-fold) set forth under the Food Quality Protection Act (FQPA) of 1996, which safeguards against potential special sensitivity in infants and children to specific residues in food or to compensate for an incomplete database (Equation (2)).

For pesticides with demonstrated potential for carcinogenic and genotoxic effects, an Oral Slope Factor (OSF) may be derived. An OSF is defined as, "an estimate of the increased cancer risk from oral exposure to a dose of 1 mg/kg-day for a lifetime. The OSF can be multiplied by an estimate of lifetime exposure (in mg/kg-day) to estimate the lifetime cancer risk" (U.S. EPA, 2011). OSFs are commonly based on tumor incidences observed in laboratory animals after long-term chemical exposure. A risk level of 10^{-5} was utilized for the present study, indicating a risk of one additional occurrence of cancer per one hundred thousand people (Equation (3)), consistent with regulatory guidance (U.S. EPA, 2005b).

For pesticides lacking sufficient toxicological data from which chemical-specific criteria could be defined, the Threshold of Toxicological Concern (TTC) approach may be applied. The TTC is based on the principle of establishing a conservative threshold below which there is no appreciable risk to human health (Kroes et al., 2004). This paradigm has been widely accepted for more than 20 years and utilized by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), EFSA, Scientific Committee on Consumer Safety (SCCS), U.S. FDA, European Medicines Agency (EMA), and World Health Organization (WHO). Further, EFSA/WHO (2016) recently reviewed and affirmed the TTC approach.

$$\text{ADI, RfD, or TDI (mg/kg-day)} = \text{NOAEL, LOAEL, or BMDL (mg/kg-day)/UF} \quad (1)$$

$$\text{PAD (mg/kg-day)} = \text{RfD (mg/kg-day)/FQPA Safety Factor} \quad (2)$$

$$10^{-5}\text{ risk level (mg/kg-day)} = 0.00001/\text{OSF (mg/kg-day)}^{-1} \quad (3)$$

2.3. Human health safety criteria databases

Multiple databases were searched to identify PADs, ADIs, TDIs, and OSFs derived by international authoritative-bodies to use in the present study to derive MALs. Chemical-specific human health effects criteria established by the U.S. EPA were obtained from data published in the Federal Register (Federal Register, 2017) and Integrated Risk Information System (IRIS) database (U.S. EPA, 2017b). Criteria established by the EU were obtained from the EU Pesticides Database (EU, 2017) and WHO Inventory of Evaluations Performed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) (WHO, 2017). Finally, criteria established by the Australian Pesticides and Veterinary Medicines Authority (APVMA) were identified within the ADI List for Agricultural and Veterinary Chemicals (APVMA, 2017).

2.4. MAL derivation procedure

Two approaches were considered for deriving MALs in the present study:

1. Conversion of existing, authoritative-body human health effects criteria
2. Application of the TTC approach for pesticides lacking human health effects criteria established by authoritative-bodies and/or toxicological data

2.4.1. Conversion of existing, authoritative-body human health effects criteria to MALs

In the event that multiple PADs, ADIs, TDIs, and/or OSFs were identified for a pesticide and the criteria were not equivalent, deference was given to the most recent criterion established by the U.S. EPA, when available. If the U.S. EPA established both a PAD and OSF, the criterion resulting in the most conservative, scientifically-defensible, MAL was used. If criterion had not yet been established by the U.S. EPA, available assessments from other authoritative-bodies were reviewed to select the most scientifically-defensible assessment. The various factors considered to select the most scientifically-defensible assessment included, but were not limited to, completeness of the data review, year of completion, risk assessment methodology applied, and species and route(s) of exposure.

The calculation used to derive the MAL was dependent on whether a PAD, ADI, TDI or 10^{-5} risk level was identified. If a PAD, ADI, or TDI was selected, the value was multiplied by the weight of an average adult (70 kg) and a Relative Source Contribution (RSC) (Equation (4)). The RSC is utilized to ensure that the established risk values are not exceeded when other non-dietary supplement sources of exposure to the chemical are considered. The RSC should be derived from chemical-specific data, when available. Alternatively, if adequate data are lacking, default RSC are recommended. For example, the U.S. EPA recommends applying a default RSC of 20% for non-drinking water sources when deriving ambient water quality criteria (U.S. EPA, 2000). As dietary supplements most commonly represent a minimal portion of the daily diet, an RSC of 10%, which assumes that 90% of exposure to a chemical occurs from sources other than dietary supplements, was applied in the present study. If a 10^{-5} risk level was selected to derive an MAL, the value was multiplied by the weight of an average adult (70 kg) (Equation (5)). According to the U.S. EPA (2000), an RSC is not applied for carcinogens that are evaluated based on linear low-dose extrapolation; therefore, MALs derived using carcinogenic hazard criteria (10^{-5} risk level) were not multiplied by an RSC in the present study.

2.4.2. Application of the TTC approach for pesticides lacking existing, authoritative-body human health effects criteria and/or toxicological data

For pesticides without existing, authoritative-body, human health effects criteria and/or toxicological data from which criteria could be derived, the TTC approach was considered in the present study. Categories excluded from the TTC paradigm and requiring chemical-specific risk assessments include high potency carcinogens, inorganic chemicals, metals (including essential metals and organometallics), organo-silicon compounds, proteins, steroids, substances known/predicted to bioaccumulate, insoluble nanomaterials, and radioactive substances (Kroes et al., 2004). MALs were calculated by multiplying the TTC value by an RSC of 10% (Equation (6)).

$$\text{MAL (mg/day)} = [\text{PAD, ADI, TDI (mg/kg-day)} \times 70\text{ kg}] \times 0.1\text{ (RSC)} \quad (4)$$

$$\text{MAL (mg/day)} = 10^{-5}\text{ risk level (mg/kg-day)} \times 70\text{ kg} \quad (5)$$

$$\text{MAL (mg/day)} = \text{TTC (µg/day)} \times 0.1\text{ (RSC)} \quad (6)$$

3. Results

In the current study, exposure-based chemical-specific MALs were derived for 185 pesticides included on the USDA Prohibited Pesticides List. Table 1 provides the 1) MALs (represented as two significant figures), 2) the source for the carcinogenic (10^{-5} risk level) or non-carcinogenic (PAD, ADI or TDI) human health effects criteria used to derive the MALs, and 3) the year the chemical dataset and resultant human health effects criteria were last evaluated. Every effort was made to obtain the most recent pesticide evaluation to derive the MAL; however, it is important to note, that there were instances when scheduled reassessments failed to occur due to pesticide discontinuation by the manufacturer, pesticides no longer present in the marketplace, and/or lack of resources at the agencies available to conduct the reassessment.

When possible, pesticides were listed with their unique Chemical Abstracts Service (CAS) number. The CAS number was left blank in instances where a unique CAS number was not identified. Similarly, multiple CAS numbers were provided for mixtures and/or parent compounds and their metabolites, where appropriate. Additionally, although iprodione metabolite isomer is included on the NOP list, it was determined that it did not meet the initial criteria of a pesticide that can

Table 1
Chemical-specific maximum allowable levels (MALs) for pesticide residues in dietary supplements.

Pesticide	CAS#	Source	Year	Non-Cancer[a] or Cancer[b] Criteria	MAL (μg/day)[c]
Total: 1-Naphthol +	90-15-3	U.S. EPA	2007	PAD	70
Carbaryl	63-25-2				
Total: 3-Hydroxycarbofuran +	16655-82-6	U.S. EPA	2007	PAD	0.42
Carbofuran	1563-66-2				
Total: 5-Hydroxythiabendazole +	948-71-0	U.S. EPA	2015	PAD	230
Thiabendazole	148-79-8				
Acephate	30560-19-1	U.S. EPA	2006	PAD	8.4
Acetamiprid	135410-20-7	U.S. EPA	2013	PAD	500
Acetochlor	34256-82-1	U.S. EPA	2013	PAD	140
Total: Aldicarb +	116-06-3	U.S. EPA	1993	PAD	7
Aldicarb sulfone +	1646-88-4				
Aldicarb sulfoxide	1646-87-3				
Allethrin	584-79-2	U.S. EPA	2009	PAD	56
Atrazine	1912-24-9	U.S. EPA	2006	PAD	13
Azinphos-methyl	86-50-0	U.S. EPA	2006	PAD	10
Azoxystrobin	131860-33-8	U.S. EPA	2012	PAD	1300
Bendiocarb	22781-23-3	U.S. EPA	1999	PAD	2.8
Bifenazate	149877-41-8	U.S. EPA	2014	PAD	70
Bifenthrin	82657-04-3	U.S. EPA	2012	PAD	70
Bitertanol	55179-31-2	U.S. EPA	2005	PAD	15
Boscalid	188425-85-6	U.S. EPA	2010	PAD	1500
Bromacil	314-40-9	U.S. EPA	1996	PAD	700
Buprofezin	69327-76-0	U.S. EPA	2012	PAD	23
Total: Captan +	133-06-2	U.S. EPA	1999	10^{-5} risk	290
Tetrahydrophthalimide (THPI)	27813-21-4				
Carbendazim (MBC)	10605-21-7	U.S. EPA	2002	PAD	18
Chlorantraniliprole	500008-45-7	U.S. EPA	2010	PAD	11000
Total: alpha-Chlordane +	5103-71-9	U.S. EPA	1998	10^{-5} risk	2
gamma-Chlordane +	5566-34-7				
trans-Chlordane +	5103-74-2				
cis-Nonachlor +	5103-73-1				
trans-Nonachlor	39765-80-5				
Chlorfenapyr	122453-73-0	U.S. EPA	2014	PAD	350
Chlorothalonil	1897-45-6	U.S. EPA	1999	10^{-5} risk	91
Chlorpropham	101-21-3	U.S. EPA	2002	PAD	350
Chlorpyrifos	2921-88-2	U.S. EPA	2014	PAD	5.5
Chlorpyrifos-methyl	5598-13-0	U.S. EPA	2015	PAD	2.3
Clofentezine	74115-24-5	U.S. EPA	2005	10^{-5} risk	19
Clopyralid	1702-17-6	U.S. EPA	2012	PAD	1100
Clothianidin	210880-92-5	U.S. EPA	2012	PAD	690
Coumaphos	56-72-4	U.S. EPA	2007	PAD	2.1
Cyazofamid	120116-88-3	U.S. EPA	2012	PAD	6600
Cycloate	1134-23-2	U.S. EPA	2004	PAD	35
Cyfluthrin	68359-37-5	U.S. EPA	2007	PAD	170
Total: Cyhalothrin:	68085-85-8	U.S. EPA	2002	PAD	7
lambda-Cyhalothrin +	91465-08-6				
R157836 epimer	N/A				
Cypermethrin	52315-07-8	U.S. EPA	2006	PAD	420
Cyprodinil	121552-61-2	U.S. EPA	2015	PAD	190
Cyromazine	66215-27-8	U.S. EPA	2014	PAD	3500
Dacthal (DCPA)	1861-32-1	U.S. EPA	1994	PAD	70
o,p'-DDD	53-19-0	N/A	N/A	N/A	0[d]
p,p'-DDD	72-54-8	U.S. EPA	1988	10^{-5} risk	2.9
o,p'-DDE	3424-82-6	N/A	N/A	N/A	0[d]
p,p'-DDE	72-55-9	U.S. EPA	1988	10^{-5} risk	2.1
o,p'-DDT	789-02-6	JMPR	2002	TDI	70
p,p'-DDT	50-29-3	U.S. EPA	1987	10^{-5} risk	2.1
Total: Deltamethrin +	52918-63-5	U.S. EPA	2015	PAD	110
Tralomethrin	66841-25-6				

(*continued on next page*)

Table 1 (*continued*)

Pesticide	CAS#	Source	Year	Non-Cancer[a] or Cancer[b] Criteria	MAL (μg/day)[c]
Total: Diazinon +	333-41-5	U.S. EPA	2006	PAD	1.4
Diazoxon (Diazinon oxon)	962-58-3				
Dichlorvos (DDVP)	62-73-7	U.S. EPA	2006	PAD	3.5
Dicloran (DCNA)	99-30-9	U.S. EPA	2006	PAD	18
Total: o,p'-Dico + B197fol +	10606-46-9	U.S. EPA	2016	PAD	2.8
p,p'-Dicofol	115-32-2				
Dieldrin	60-57-1	U.S. EPA	1988	10^{-5} risk	0.044
Difenoconazole	119446-68-3	U.S. EPA	2010	PAD	70
Diflubenzuron	35367-38-5	U.S. EPA	2007	PAD	140
Dimethoate	60-51-5	U.S. EPA	2006	PAD	15
Dimethomorph	110488-70-5	U.S. EPA	2014	PAD	700
Dinotefuran	165252-70-0	U.S. EPA	2013	PAD	7000
Diphenamid	957-51-7	U.S. EPA	1987	PAD	210
Diphenylamine (DPA)	122-39-4	U.S. EPA	2005	PAD	700
Total: Disulfoton +	298-04-4	U.S. EPA	2006	PAD	0.91
Disulfoton-sulfone	2497-06-5				
Diuron	330-54-1	U.S. EPA	2003	PAD	3.7
Total: Endosulfan:	115-29-7	U.S. EPA	2010	PAD	42
alpha-Endosulfan +	959-98-8				
beta-Endosulfan +	33213-65-9				
Endosulfan sulfate	1031-07-8				
Endrin	72-20-8	U.S. EPA	1988	PAD	2.1
Total: Esfenvalerate +	66230-04-4	U.S. EPA	2004	PAD	13
Fenvalerate	51630-58-1				
Ethephon	16672-87-0	U.S. EPA	2006	PAD	420
Ethion	563-12-2	U.S. EPA	2001	PAD	3.5
Ethoprop	13194-48-4	U.S. EPA	2006	PAD	9.8
Ethoxyquin	91-53-2	U.S. EPA	2004	PAD	140
Etoxazole	153233-91-1	U.S. EPA	2011	PAD	320
Famoxadone	131807-57-3	U.S. EPA	2008	PAD	9.8
Fenamidone	161326-34-7	U.S. EPA	2011	PAD	200
Total: Fenamiphos +	22224-92-6	U.S. EPA	2002	PAD	0.7
Fenamiphos sulfone +	31972-44-8				
Fenamiphos sulfoxide	31972-43-7				
Fenarimol	60168-88-9	U.S. EPA	2010	PAD	42
Fenbuconazole	114369-43-6	U.S. EPA	2008	10^{-5} risk	200
Fenhexamid	126833-17-8	U.S. EPA	2007	PAD	1200
Fenpropathrin	39515-41-8	U.S. EPA	2013	PAD	120
Fenpyroximate	134098-61-6	U.S. EPA	2012	PAD	350
Fenthion	55-38-9	U.S. EPA	2001	PAD	0.49
Fipronil	120068-37-3	U.S. EPA	2007	PAD	1.4
Flonicamid	158062-67-0	U.S. EPA	2012	PAD	280
Fludioxonil	131341-86-1	U.S. EPA	2015	PAD	2300
Fluoxastrobin	361377-29-9	U.S. EPA	2012	PAD	110
Fluridone	59756-60-4	U.S. EPA	2012	PAD	1100
Flutolanil	66332-96-5	U.S. EPA	2010	PAD	3500
Fluvalinate	69409-94-5	U.S. EPA	2005	PAD	35
Folpet	133-07-3	U.S. EPA	2012	PAD	630
Fonofos	944-22-9	U.S. EPA	1999	PAD	14
Formetanate hydrochloride	23422-53-9	U.S. EPA	2010	PAD	2.2
gamma-Hexachlorcyclohexanum (lindane)	58-89-9	U.S. EPA	2002	PAD	11
Heptachlor epoxide	1024-57-3	U.S. EPA	1987	10^{-5} risk	0.077
Hexachlorobenzene (HCB)	118-74-1	U.S. EPA	2008	10^{-5} risk	0.69
alpha-Hexachlorocyclohexane	319-84-6	U.S. EPA	1987	10^{-5} risk	0.11
Hexaconazole	79983-71-4	U.S. EPA	1999	10^{-5} risk	44
Hexythiazox	78587-05-0	U.S. EPA	2012	PAD	180
Hydroprene	41096-46-2	U.S. EPA	1997	PAD	700
Imazalil	35554-44-0	U.S. EPA	2002	10^{-5} risk	11
Imidacloprid	138261-41-3	U.S. EPA	2010	PAD	400
Indoxacarb	173584-44-6	U.S. EPA	2013	PAD	140
Iprodione	36734-19-7	U.S. EPA	2012	10^{-5} risk	16
Iprodione metabolite isomer	63637-89-8	N/A	NA	NA	0[e]
Linuron	330-55-2	U.S. EPA	2008	PAD	54
Total: Malathion +	121-75-5	U.S. EPA	2016	PAD	70
Malaoxon	1634-78-2				
Metalaxyl	57837-19-1	U.S. EPA	2016	PAD	3500
Methamidophos	10265-92-6	U.S. EPA	2006	PAD	0.7
Methidathion	950-37-8	U.S. EPA	1999	PAD	11
Methiocarb	2032-65-7	U.S. EPA	1994	PAD	35
Methomyl	16752-77-5	U.S. EPA	2007	PAD	11
Methoxychlor	72-43-5	U.S. EPA	1990	PAD	35
Methoxyfenozide	161050-58-4	U.S. EPA	2012	PAD	700
Metolachlor	51218-45-2	U.S. EPA	1995	PAD	700
Metribuzin	21087-64-9	U.S. EPA	1998	PAD	91
Mevinphos	7786-34-7	U.S. EPA	2000	PAD	0.18

(*continued on next page*)

Table 1 (*continued*)

Pesticide	CAS#	Source	Year	Non-Cancer[a] or Cancer[b] Criteria	MAL (μg/day)[c]
MGK-264	113-48-4	U.S. EPA	2006	PAD	430
Myclobutanil	88671-89-0	U.S. EPA	2007	PAD	180
Naled	300-76-5	U.S. EPA	2001	PAD	14
Napropamide	15299-99-7	U.S. EPA	2005	PAD	840
Total: Norflurazon +	27314-13-2	U.S. EPA	2001	PAD	110
Norflurazon desmethyl	23576-24-1				
Omethoate	1113-02-6	U.S. EPA	2006	PAD	5.1
Oxadixyl	77732-09-3	APVMA	1988	ADI	70
Total: Oxamyl +	23135-22-0	U.S. EPA	2007	PAD	7
Oxamyl oxime	30558-43-1				
Oxydemeton-methyl sulfone	17040-19-6	U.S. EPA	1999	PAD	0.88
Parathion-methyl	298-00-0	U.S. EPA	2006	PAD	0.14
Pendimethalin	40487-42-1	U.S. EPA	2012	PAD	2100
Total: Pentachloroaniline (PCA) +	527-20-8	U.S. EPA	2005	PAD	7
Pentachlorothioanisole (PCTA) +	1825-19-0				
Quintozene (PCNB)	82-68-8				
Pentachlorobenzene (PCB)	608-93-5	U.S. EPA	1987	PAD	5.6
Permethrin	52645-53-1	U.S. EPA	2009	10^{-5} risk	73
Phenmedipham	13684-63-4	U.S. EPA	2005	PAD	1700
o-Phenylphenol	90-43-7	EFSA/EU	2008	ADI	2800
Total: Phorat sulfone +	2588-04-7	U.S. EPA	2006	PAD	1.2
Phorate sulfoxide	2588-03-6				
Phosalone	2310-17-0	U.S. EPA	2006	PAD	14
Phosmet	732-11-6	U.S. EPA	2010	PAD	42
Piperonyl butoxide	51-03-6	U.S. EPA	2005	PAD	1100
Pirimicarb	23103-98-2	EFSA/EU	2014	ADI	250
Pirimiphos-methyl	29232-93-7	U.S. EPA	1999	PAD	0.49
Prallethrin	23031-36-9	U.S. EPA	2014	PAD	56
Prochloraz	67747-09-5	U.S. EPA	1989	10^{-5} risk	4.7
Procymidone	32809-16-8	U.S. EPA	2005	10^{-5} risk	30
Prometryn	7287-19-6	U.S. EPA	2009	PAD	280
Pronamide	23950-58-5	U.S. EPA	2015	PAD	280
Propargite	2312-35-8	U.S. EPA	2001	10^{-5} risk	210
Propiconazole	60207-90-1	U.S. EPA	2013	PAD	700
Pymetrozine	123312-89-0	U.S. EPA	2010	PAD	56
Pyraclostrobin	175013-18-0	U.S. EPA	2009	PAD	240
Pyridaben	96489-71-3	U.S. EPA	2005	PAD	35
Pyrimethanil	53112-28-0	U.S. EPA	2012	PAD	1200
Pyriproxyfen	95737-68-1	U.S. EPA	2012	PAD	2500
Quinoxyfen	124495-18-7	U.S. EPA	2009	PAD	1400
Resmethrin	10453-86-8	U.S. EPA	2016	10^{-5} risk	12
Simazine	122-34-9	U.S. EPA	2006	PAD	13
Spinetoram	187166-40-1 (Spinetoram J)	U.S. EPA	2010	PAD	170
	187166-15-0 (Spinetoram L)				
Total: Spiromesifen parent + Enol metabolite	283594-90-1	U.S. EPA	2012	PAD	150
Sulfentrazone	122836-35-5	U.S. EPA	2014	PAD	980
Tebuconazole	107534-96-3	U.S. EPA	2011	PAD	200
Tebufenozide	112410-23-8	U.S. EPA	2008	PAD	140
Tetrachlorvinphos	22248-79-9	U.S. EPA	2002	PAD	290
Tetradifon	116-29-0	APVMA	1990	ADI	140
Thiacloprid	111988-49-9	U.S. EPA	2003	10^{-5} risk	17
Thiamethoxam	153719-23-4	U.S. EPA	2011	PAD	84
Thiobencarb	28249-77-6	U.S. EPA	2011	PAD	70
Thiodicarb	59669-26-0	U.S. EPA	1998	10^{-5} risk	37
Triadimefon	43121-43-3	U.S. EPA	2009	PAD	240
Triadimenol	55219-65-3	U.S. EPA	2006	PAD	24
Tribufos (DEF)	78-48-8	U.S. EPA	2006	PAD	0.7
Trifloxystrobin	141517-21-7	U.S. EPA	2011	PAD	270
Triflumizole	68694-11-1	U.S. EPA	2009	PAD	82
Trifluralin	1582-09-8	U.S. EPA	2004	10^{-5} risk	120
Vinclozolin	50471-44-8	U.S. EPA	2000	PAD	8.4

Equation (4): MAL (mg/day) = [PAD, ADI, or TDI (mg/kg-day) x 70 kg] x 0.1 (RSC).
Equation (5): MAL (mg/day) = 10^{-5} risk level (mg/kg-day) x 70 kg.
Equation (6): MAL (mg/day) = TTC (μg/day) x 0.1 (RSC).
U.S. EPA = United States Environmental Protection Agency.
JMPR = Joint FAO/WHO Meeting on Pesticide Residues.
APVMA = Australian Pesticides and Veterinary Medicines Authority.
EFSA = European Food Safety Authority.
EU = European Union.

[a] Non-Cancer includes population adjusted dose (PAD), acceptable daily intake (ADI), and tolerable daily intake (TDI).
[b] Cancer criteria includes 10^{-5} risk level.
[c] The calculation used to derive the MAL was dependent on whether a PAD, ADI, TDI, 10^{-5} risk level, or Threshold of Toxicological Concern (TTC) was selected.
[d] A chemical-specific risk assessment is required to establish an MAL.
[e] Due to lack of reliable test methodology procedure, an MAL was not established for this metabolite isomer.

be reliably analytically analyzed as a reference standard was not identified. Consequently, an MAL was not derived for iprodione metabolite isomer, and a default MAL of zero was assigned according to the zero tolerance regulation (Table 1).

Utilizing the first approach of converting existing, authoritative-body human health effects criteria to MALs, the most recent PAD or OSF established by the U.S. EPA was identified for 177 of the 185 pesticides (96%). The human health effects criteria were converted to MALs using Equations (4) and (5) (Table 1). Some human health effects criteria established by the U.S. EPA applied to more than one pesticide for reasons including, but not limited to, two or more isomeric chemicals, technical mixtures, or parent compounds and their metabolites. In such cases, cumulative groups were constructed and assigned a single, group MAL.

Additionally, if both a PAD and an OSF were established by the U.S. EPA, the criterion resulting in the most conservative, scientifically-defensible, MAL was used. Five pesticides had an established PAD and OSF where the calculated 10^{-5} risk level value was lower than the PAD value; however, the MAL derived using the PAD criteria was more conservative (Table 2). This was a result of applying a 10% RSC to MALs derived using non-carcinogenic human health effects criteria (Equation (4)). Consequently, the non-cancerous human health effects endpoints (in these cases, the PAD) were used to derive the MALs for the five pesticides. Of the 177 pesticide MALs derived using criteria established by the U.S. EPA, 28 MALs were derived using carcinogenic human health effects endpoints (Equation (5)).

U.S. EPA human health effects criteria were not identified for a total of seven pesticides (o-phenylphenol, oxadixyl, tetradifon, o,p'-DDT, pirimicarb, o,p'-DDD and o,p'-DDE) for reasons including, but not limited to, pesticide discontinuation, voluntary pesticide registration cancellation, and/or banned for use in the U.S. However, the EFSA, WHO JMPR, and/or APVMA established human health effects criteria for five of these pesticides (o-phenylphenol, oxadixyl, tetradifon, o,p'-DDT, and pirimicarb). Health effects criteria for four of these pesticides (o-phenylphenol, oxadixyl, tetradifon and o,p'-DDT) were established by only one other authoritative-body. An ADI was established for o-phenylphenol by the EFSA, APVMA derived ADIs for oxadixyl and tetradifon, and the WHO JMPR derived a provisional TDI (PTDI) for o,p'-DDT. Pirimicarb had three different ADIs established by the EFSA, WHO JMPR and APVMA. A review of the publicly available assessments supported the ADI derived by EFSA (listed in the EU database) as the most robust criteria as it was the most recent analysis and was the only analysis based on a chronic, repeat-dose, toxicity study. The ADIs and PTDI identified for these five pesticides were used to derive their respective MALs reported in Table 1.

Criteria established by the U.S. EPA, EFSA, WHO JMPR, and APVMA were not identified for o,p'-DDD and o,p'-DDE. The second approach (Equation (6)), application of TTC, was not appropriate because the chemicals fall into an exclusion category (e.g., chemicals with bioaccumulative potential) and adequate toxicological data exist. A chemical-specific risk assessment would be required in order to establish human health effects criteria and subsequently derive MALs for these chemicals. Therefore, MALs were not derived for these two pesticides in the present study; their respective MALs are listed as zero in Table 1.

Table 2
Comparison of pesticides Maximum Allowable Levels (MALs) derived using both carcinogenic and non-carcinogenic human health effects criteria.

Pesticide	CAS #	MAL (μg/day) using 10^{-5} risk level	MAL (μg/day) using PAD criteria
Total: 1-Naphthol + Carbaryl	90-15-3 63-25-2	800	70
Ethoprop	13194-48-4	25	9.8
Pymetrozine	123312-89-0	59	56
Tetrachlorvinphos	22248-79-9	380	290

4. Discussion

Given that many botanicals do not have established pesticide tolerances or action levels and are subject to zero tolerance regulation, there has been a renewed interest in developing science-informed pesticide tolerances or action levels. One methodology was proposed by the U.S. Pharmacopeia (USP) Convention, which issued a stimuli article expressing the need for clear, rational regulations for articles of botanical origin (USP, 2016). The recommendation was to utilize the limits established in USP-New Formulary (USP-NF) Monographs and USP General Chapter 561 (2015) for botanical drugs, for all botanical articles of commerce (including foods), which do not have tolerances established by the U.S. EPA. The pesticide residue limits in General Chapter 561 (2015) are based on tolerable levels or GAPs for the pesticides. When data are not available regarding achievable limits for GAPs, the ADI established by the Food and Agriculture Organization (FAO)/WHO is utilized (USP, 2016). However, establishing pesticide residue limits based on GAPs instead of evidence-based methodologies, may result in limits that are unnecessarily conservative.

While the methodology proposed by USP helps harmonize the evaluation of pesticides for all botanical articles of commerce, a benefit to the science-informed methodology proposed within the present study is its broad applicability. The current study has a small sample size; however, this methodology can be applied to all pesticides with established human health effects criteria. This broad applicability would minimize the reliance on precautionary zero tolerance and GMRLs. The general limits present in current regulations assume that there is a risk associated with exposure to a pesticide residue without consideration of the exposure and scientific data to support the assumed risk. Furthermore, unavoidable NPS pesticide contamination could be evaluated to chemical-specific MALs instead of relying on zero tolerance and GMRLs (40 CFR Part 180.5; Health Canada, 2017; EC, 2008; USP, 2016). Evaluating pesticides to chemical-specific MALs, based on publicly-available scientific data, results in a more confident, science- and health effects-based risk management decision rather than assuming any exposure to a pesticide residue poses a statistically or biologically significant risk to human health. The approach described herein protects public health and safety while allowing for evaluation of dietary supplements containing botanical dietary ingredients for pesticide residues from intentional pesticide applications and unavoidable NPS pesticide contamination.

Additionally, within this approach, a chemical-specific risk assessment may be conducted for pesticides with adequate toxicological data to establish human health effects criteria, if criteria have not already been established, and subsequently, an MAL may be derived. For pesticides lacking toxicological data, the TTC may be utilized in order to derive an MAL. The TTC is based on the principle of establishing a conservative threshold below which there is no appreciable risk to human health by utilizing toxicological data from chemicals with related chemical structures (Kroes et al., 2004). There are limitations to applying TTC to some substances, such as those known/predicted to bioaccumulate (e.g. o,p'-DDD and o,p'-DDE), but in such cases, a chemical-specific risk assessment could be conducted to establish human health effects criteria. Consequently, within this methodology an MAL can be derived for any pesticide.

The current U.S., Canadian and EU pesticide regulations rely on the concentration of a pesticide residue allowed to remain in or on each treated food commodity (EPA, 2017; Health Canada, 2015; EC, 2008; EC, 2017). These regulations are only partially harmonized and differ in how they address pesticide-crop combinations lacking an established tolerance or action level, with the U.S. utilizing a precautionary zero tolerance approach and the EU and Canada developing GMRLs of 0.01 ppm and 0.1 ppm, respectively. Of note, the current U.S., Canadian

and EU regulations are based on chemical concentrations in or on food commodities; whereas, the proposed MALs are based on human health effects criteria which provide human exposure limits. This fundamental difference prevents a direct comparison between the concentration-based MRLs and the exposure-based MALs; however, by multiplying the analytically detected concentration of the pesticide in or on a dietary supplement by the serving size (dry metric weight) and servings per day for the dietary supplement, the result can be directly compared to the chemical-specific MAL. Therefore, while it is beyond the scope of this analysis to convert the MALs to concentration-based values, the approach presented in this study offers an opportunity to use existing human health effects evaluations to derive chemical-specific exposure-based limits which are applicable to pesticides found in all food products.

A notable limitation of the methodology proposed herein is the lack of exposure data for pesticides in dietary supplements containing botanical dietary ingredients to allow for the establishment of a data-driven RSC. As dietary supplements commonly represent a minimal portion of the daily diet on a mg/kg basis, an RSC of 10% was applied in the present study, which assumes that 90% of possible exposure to a pesticide occurs from sources outside of dietary supplements. It is professional judgment that a 10% RSC would not significantly increase the risk of exposure to pesticides in dietary supplements containing botanical dietary ingredients, although there are not sufficient data available to fully support the assertion that an RSC of 10% is sufficiently conservative.

5. Conclusion

Current U.S., Canadian and EU pesticide regulations are insufficient to address the potential risk associated with exposure to pesticide residues in or on botanical dietary ingredients in dietary supplements. The current study utilized human health effects criteria derived by U.S. and international authoritative-bodies to develop chemical-specific, science-informed MALs that can be applied to all food commodities, including botanical dietary ingredients. While acknowledging that this methodology would be an alternate approach to the partially-harmonized international regulations speaking to pesticide residues, the broad applicability of this methodology minimizes reliance on the provisional zero tolerance and GMRLs that are currently enforced, addresses intentional pesticide applications and unavoidable NPS pesticide contamination, and remains protective of public health and safety.

Conflicts of interest

NSF International, an independent, global, not-for-profit public health organization, certifies dietary supplements to NSF/ANSI 173 (2016). The manuscript is based on the methodology developed for deriving MALs for pesticides included in NSF/ANSI 173. The authors of the manuscript have no conflicts to disclose.

Acknowledgments

The authors appreciate our colleagues from NSF International including A. Phelka, K. Cox, and S. Laman and the members who voluntarily participated in the NSF/ANSI 173-Dietary Supplements Joint Committee Pesticides Task Group for providing feedback throughout the development of the methodology for deriving MALs.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2018.11.045.

References

40 CFR 180.101(c). Tolerances and Exemptions for Pesticide Chemicals in or on Raw Agricultural Commodities. Specific Tolerances; general provisions. Available at:: https://www.gpo.gov/fdsys/pkg/CFR-2002-title40-vol20/pdf/CFR-2002-title40-vol20-sec180-101.pdf (accessed July 27, 2017).

40 CFR Part 180. Tolerances and exemptions for pesticide chemicals in or on raw agricultural commodities. Available at: https://www.ecfr.gov/cgi-bin/text-idx?SID=726260819680793146f1130f1e0109f&mc=true&node=pt40.26.180&rgn=div5 (accessed July 27, 2017).

40 CFR Part 180.5. Tolerances and Exemptions from Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities. Zero Tolerances. Available at: https://www.gpo.gov/fdsys/pkg/CFR-1996-title40-vol11/pdf/CFR-1996-title40-vol11-sec180-5.pdf (accessed July 27, 2017).

Australian Government DOH (Department of Health), 2017. Acceptable daily intakes for agricultural and veterinary chemicals. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/ocs-adi-list.htm, Accessed date: 3 November 2017.

Council for Responsible Nutrition, 2016. CRN 2016 annual Survey on dietary supplements. Available at: https://www.crnusa.org/resources/crn-2016-annual-survey-dietary-supplements, Accessed date: 26 February 2018.

Council for Responsible Nutrition, 2017. CRN 2017 annual Survey on dietary supplements. Available at: https://www.crnusa.org/resources/crn-2017-annual-survey-dietary-supplements, Accessed date: 26 February 2018.

Dietary Supplement Health and Education Act. 1994. Pub L No. 103-417. 103rd Congress, 2nd sess., S784.

Dunham, J., Associates, 2016. 2016 economic impact of the dietary supplement industry. Prepared for: council for responsible nutrition. Available at: https://nutrition.guerrillaeconomics.net/assets/site/res/CRN%20Methodology.pdf, Accessed date: 3 November 2017.

EFSA (European Food Safety Authority) and WHO (World Health Organization), 2016. Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree. In: EFSA Supporting Publication: EN-1006, 50.

European Commission, 2008. New rules on pesticide residues in food. Available at: https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_mrl_legis_factsheet_en.pdf, Accessed date: 3 November 2017.

European Commission, 2017. European Union pesticides database. Available at: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN , Accessed date: 3 November 2017.

Faustman, E., Omenn, G., 2013. Risk assessment. In: Klaassen, C.D. (Ed.), Casarett and Doull's Toxicology: the Basic Science of Poisons, eighth ed. McGraw Hill Education, New York.

Federal Food, Drug and Cosmetic Act. 1938a. P.L. 75-717. 52 Stat. 1040.

Federal Food, Drug, Act, Cosmetic, 1938b. Sec. 408 Tolerances and Exemptions for Pesticide Chemical Residues. 52 Stat. 1040.

Health Canada, 2015. Maximum Residue Limits for Pesticides. Government of Canada. Available at: https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/public/protecting-your-health-environment/pesticides-food/maximum-residue-limits-pesticides.html , Accessed date: 20 June 2017.

Health Canada, 2017. Food and Drug Regulations. Part B, Division 15. B.15.002). Government of Canada. Available at: http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/page-72.html#h-107, Accessed date: 27 July 2017.

Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Würtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem. Toxicol. 42, 65–83.

Low, T.Y., Wong, K.O., Yap, A.L.L., De Haan, LHJ, Rietjens, C.M., 2017. The regulatory framework across international jurisdictions for risks associated with consumption of botanical food supplements. Compr. Rev. Food Sci. Food Saf. 16 (5), 821–834.

NIH State-of-the-Science Panel, 2007. National institutes of health state-of-the-science conference statement: multivitamin/mineral supplements and chronic disease prevention. Am. J. Clin. Nutr. 85 (Suppl. l) 257S-64S.

NSF/ANSI 173, 2016. Dietary supplements. NSF international, ann arbor, MI. Available at: http://www.techstreet.com/nsf/standards/nsf-173-2016?product_id=1918654, Accessed date: 3 November 2017.

Office of the Federal Register, 2017. Federal register: the daily journal of the United States government. Available at: https://www.federalregister.gov/, Accessed date: 3 November 2017.

U.S. EPA (U.S. Environmental Protection Agency), 2000. Methodology for deriving ambient water quality criteria for the protection of human health. In: Office of Water, EPA-822-B-00-004.

U.S. EPA (U.S. Environmental Protection Agency), 2005a. Protecting water quality from agricultural runoff. EPA 841-F-05-001. Available at: https://nepis.epa.gov/Exe/ZyPDF.cgi/P10039OH.PDF?Dockey=P10039OH.PDF, Accessed date: 3 November 2017.

U.S. EPA (U.S. Environmental Protection Agency), 2005b. Guidelines for Carcinogen Risk Assessment. Federal Register 70:17765-17817. Available at: https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment, Accessed date: 9 November 2018.

U.S. EPA (U.S. Environmental Protection Agency), 2011. IRIS glossary. Integrated risk information System (IRIS). Available at: http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary, Accessed date: 3 November 2017.

U.S. EPA (U.S. Environmental Protection Agency), 2017a. Setting tolerances for pesticide residues in foods. Available at: https://www.epa.gov/pesticide-tolerances/setting-

tolerances-pesticide-residues-foods, Accessed date: 27 July 2017.
U.S. EPA (U.S. Environmental Protection Agency), 2017b. IRIS database. Available at: https://www.epa.gov/iris, Accessed date: 3 November 2017.
U.S. FDA (U.S. Food and Drug Administration). CPG Sec. 575.100. Pesticide Residues in Food and Feed – Enforcement Criteria. Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-ice/documents/webcontent/ucm123236.pdf (accessed June 19, 2017).
U.S. FDA (U.S. Food and Drug Administration). 21 CFR Part 509. Unavoidable contaminants in animal food and food-packaging material. Available at: https://www.ecfr.gov/cgi-bin/text-idx?SID=634d4e3f6d0a944579cd74ae683acbe7&mc=true&node=pt21.6.509&rgn=div5 (accessed June 19, 2017).
U.S. FDA (U.S. Food and Drug Administration). 21 CFR Part 101. Food labeling. Available at: https://www.ecfr.gov/cgi-bin/text-idx?SID=634d4e3f6d0a944579cd74ae683acbe7&mc=true&node=pt21.2.101&rgn=div5#sp21.2.101.a (accessed June 19, 2017).
USDA NOP (U.S. Department of Agriculture National Organic Program), 2011. Prohibited pesticides for NOP residue testing (NOP 2611-1). Available at: https://www.ams.usda.gov/sites/default/files/media/NOP-2611-1-ProhibitedPesticidesforNOPResidueTesting.pdf, Accessed date: 3 November 2017.
USDA NOP (U.S. Department of Agriculture National Organic Program), 2012. Laboratory selection criteria for pesticide residue testing. NOP-2611). Available at: https://www.ams.usda.gov/sites/default/files/media/2611.pdf, Accessed date: 3 November 2017.
USP (United States Pharmacopeia), 2015. Articles of Botanical Origin. USP 38-NF 33. United States Pharmacopeial Convention, Rockville, MD, pp. 561.
USP (United States Pharmacopeia, 2016. Stimuli to the revision process: Need for clear regulation of pesticide residue limits for articles of botanical origin. Botanical dietary supplements and herbal Medicines Expert committee (brinckmann JA, dentali S, fletcher E, gafner S, marles RJ) and USP staff (okunji C, sarma N, giancaspro GI). In: Pharmacopeial Forum 42 (2).
WHO (World Health Organization, 2017. Inventory of evaluations performed by the JMPR (Joint FAO/WHO meeting on pesticide residues). Available at: http://apps.who.int/pesticide-residues-jmpr-database, Accessed date: 3 November 2017.