CHAPTER 2

LITERATURE REVIEWS

2.1 Introduction of fungicides

Fungicides are chemicals or biological agents that inhibit the growth of fungi or fungal spores. Modern fungicides do not kill fungi, they simply inhibit growth for a period of days or weeks. Fungi can cause serious damage in agriculture, resulting in critical losses of yield, quality and profit. Fungicides are used both in agriculture and to fight fungal infections in animals. Chemicals used to control oomycetes, which are not fungi, are also referred to as fungicides as oomycetes use the same mechanisms as fungi to infect plants (Latijnhouwers et al., 2000). Fungicides can be contact, translaminar or systemic. Contact fungicides are not taken up into the plant tissue, and only protect the plant where the spray is deposited; translaminar fungicides redistribute the fungicide from the upper, sprayed leaf surface to the lower, unsprayed surface; systemic fungicides are taken up and redistributed through the xylem vessels to the upper parts of the plant.

2.2 Types of fungicides

In recent years, the total amount of the use of pesticides has increased worldwide. In Thailand, the Department of Agriculture (DOA) reported that pesticides were increased 1.2 fold in 5 year time from 110,000 tons in 2008 to 134,000 tons in 2012 and the most imported pesticides in Thailand is shown in Figure 2.1. The major abundant was herbicides, insecticides and fungicides, respectively (DOA, 2013). Fungicides are chemicals used to control the fungi which cause molds, rots and plant diseases. The most fungicides are applied over a large surface area to try to directly hit every fungus. Some fungicides may be systemic in that the plant to be protected may be fed or injected with the chemical. They can also be classified as systemic and non-systemic; systemic fungicides are present in all parts of plant after application, and in that way they offer reliable protection for a certain period. Non-systemic fungicides provide shorter protection because they degrade faster under the sunlight and rainfall (Hutson and Miyamoto, 1999).

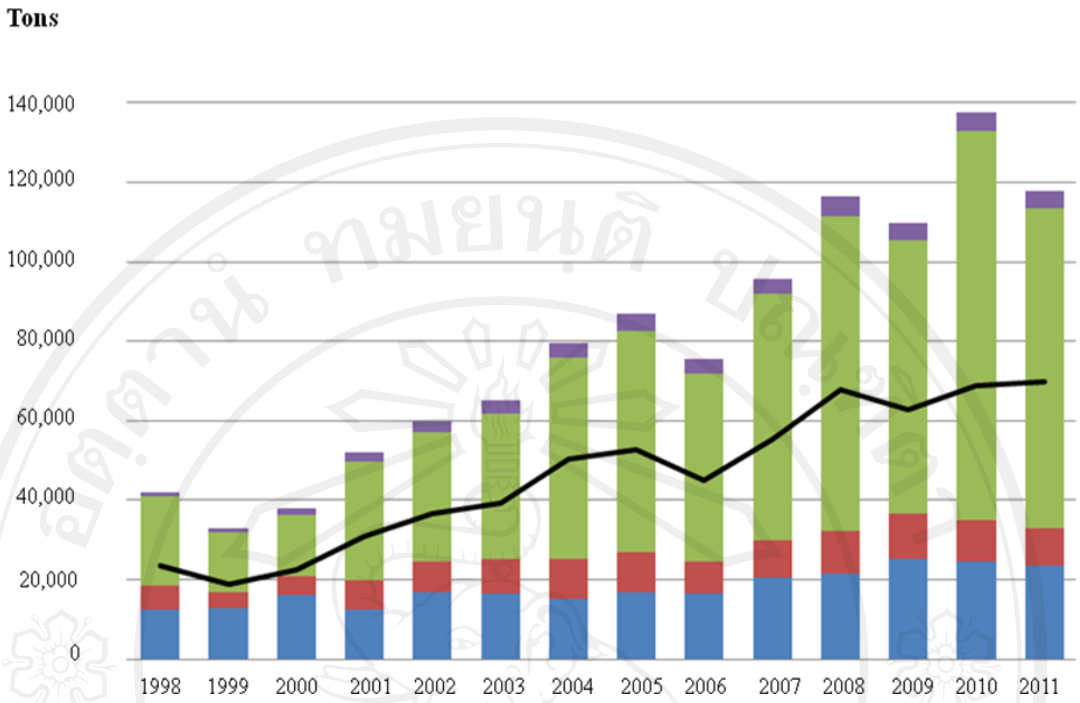


Figure 2.1 The amount of imported pesticides in Thailand (1998-2011)

Source: The Department of Agriculture (DOA)**,** Thailand.

Several classification systems based on structure appear more of a web organization than a rationalized listing. In addition to classification by chemical structural grouping, fungicides can be categorized agriculturally and horticulturally according to the mode of application (use). According to the origin of fungicides, we can classify them by using the chemical classification system shown in Table 2.1.

Table 2.1 Major chemical classes of fungicides

Groups and sub-groups	Examples
1. Halogenated substituted monocyclic aromatics	- Chorothalonil, dicloran, tecnazine, dinocap, quintozene, chloroneb, hexachlorobenzene, dichlorophen, pentachlorophenol
2. Carbamic acid derivative 2.1 Dithiocarbamates 2.2 Ethylene bisdithiocarbamates	 - Metam-sodium, ferbam, thiram, ziram - Maneb, mancozeb, zineb
3. Benzimidazoles/thiabendazole	- Benomyl, thiabendazole, thiophanate-methyl, imazalil, carbendazim, fuberidazole
4. Chloroalkylthiodicarboximides	- Captan, captafol, folpet
5. Azoles	- Cyproconazole, diniconazole, etrinazole, fenbuconazole, hexaconazole, triadimenol penconazole, terbuconazole, triadimefon,
6. Morpholines	- Dodemorph, fenpropiomorph, tridemorph
7. Carboxanilides/oxathiins	- Carboxin, oxycarboxin
8. Organophosphates	- Pyrazophos, tolclofos-methyl
9. Piperazines	- Triforine

Table 2.1 Major chemical classes of fungicides (Continued)

Chemical group	Generic name
10. Metallic	
10.1 Organometallic	- Bistributyltin oxide, cadmium succinate, copper acetate, mercury acetate, mercury benzoate, methoxyethyl mercury acetate, phenylmercury nitrile, tributyltin
10.2 Inorganic	- Bordeaux, copper chloride oxide, lime sulfur, colloidal sulfur
11. Miscellaneous	
11.1 Aliphatic aldehydes	- Acrolein
11.2 Thiocarbonate	- Sodium tetrathiocarbonate
11.3 Antibiotics	- Cycloheximide, streptomycin, polyoxins, validamycin, blasticidin-S, kasugamycin,
10.4 Cinnamic acid derivatives	- Dimethomorph

Source: Timothy and Brian, 2004.

2.3 Mode of action

The body or thallus of most fungi exists as microscopic tubes called hyphae (Figure 2.2)

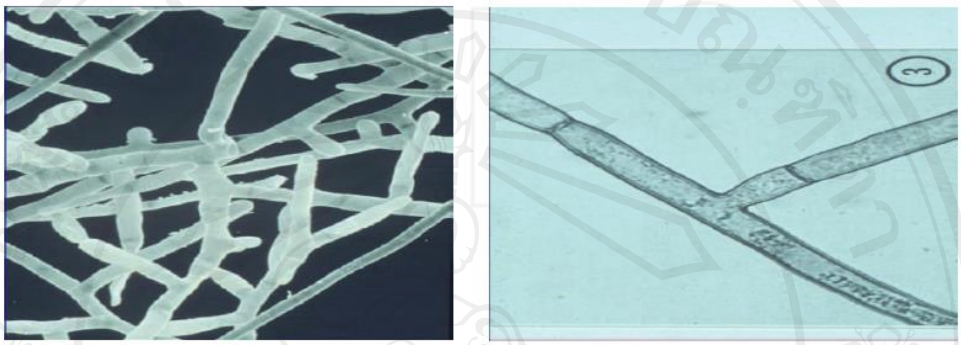


Figure 2.2 Hyphae of a fungi

Source: Burpee, 2006.

A fungal cell contains many of the same organelles as other eukaryotes (Figure 2.3).

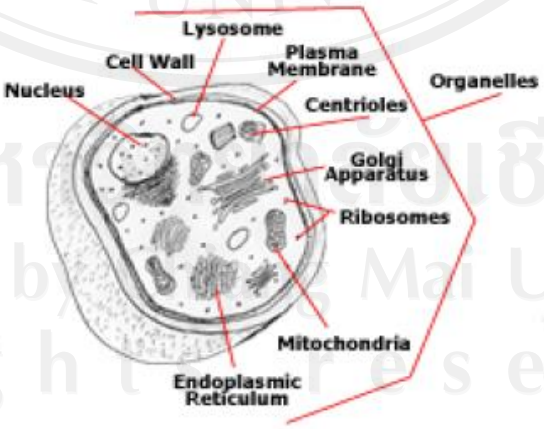


Figure 2.3 Fungal cell with organelles

Source: Foster and Smith, 2010.

Fungicides can be divided into 2 groups based on mode of action in fungal cells:

a. Site-specific inhibitors: Site-specific inhibitors target individual sites within the fungal cell (Figure 2.4).

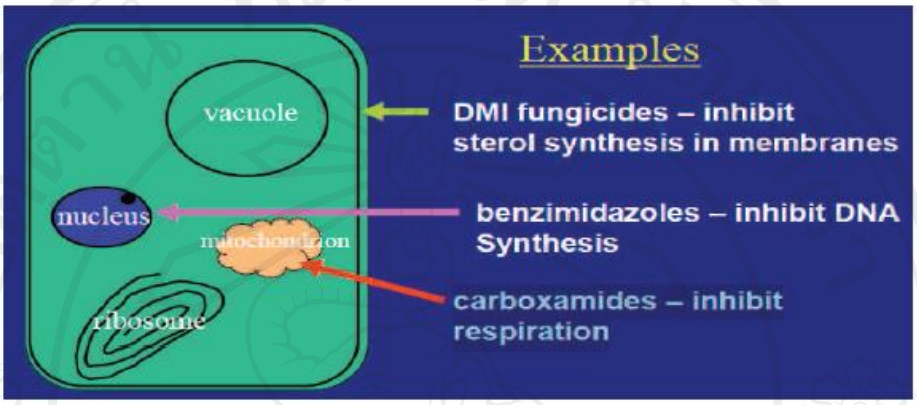


Figure 2.4 Site-Specific Inhibitors (DMI: demethylation inhibitors fungicides)

Source: Burpee, 2006.

b. Multi-site inhibitors

Multisite inhibitors target many different sites in each fungal cell (figure 2.5)

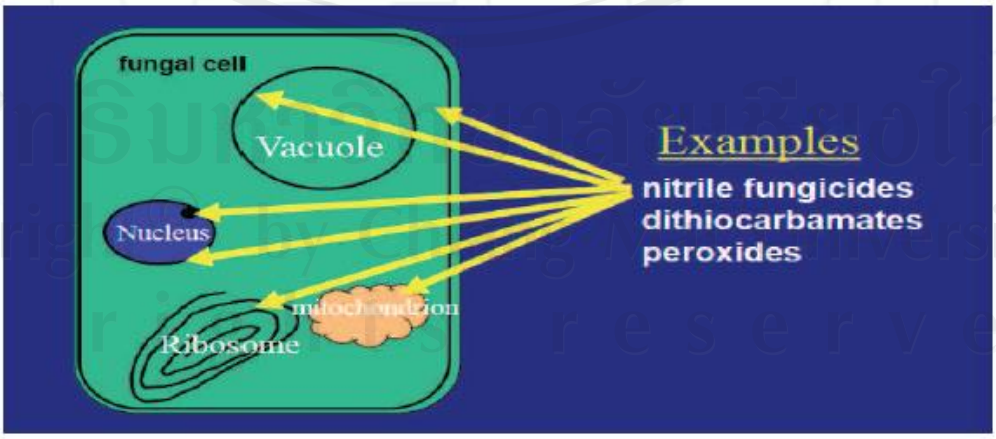


Figure 2.5 Multi-site Inhibitors

Source: Burpee, 2006.

2.4 Cabendazim

Carbendazim or methyl-2-enzimidazole carbamate is the most widely used active ingredient of the benzimidazole fungicides. It is a broad-spectrum systemic fungicide with protective and curative action. Carbendazim products are used for the control of wide range of fungal disease such as mold, spot, powdery mildew, scorch, rot, and blight in a variety of crops and carbendazim works by inhibiting the development of fungi probably by interfering with spindle formation at mitosis.

2.4.1 Toxicity of carbendazim

Carbendazim is classified by the World Health Organization (WHO) as unlikely to present hazard in normal use. The acute oral LD_{50} (dose at which half the sample is dead) for rats is >15000 mg/kg and >2500 mg/kg for dogs and it is low toxicity to rodent and non-rodent species via the oral, dermal, inhalational and intraperitoneal routes.

2.4.1.1 Reproductive effects

Carbendazim is known for a long time to cause adverse effects on the male reproductive systems, including decreased testicular and epididymal weights and reduced epididymal sperm counts and fertility in the rats. This is confirmed including Moffit et al. (2007) showed impair of sertolli cells by inhibiting microtubule assembly and loss of testicular function and Yu et al. (2009) effects in rats on spermatogenesis and fertility (meiotic transformation).

2.4.1.2 Endocrine disrupting substance

In vitro tests (Morinaga et al., 2004) show inhibition of aromatase and interference with microtubules. In vivo tests in zebrafish show inhibition of brain

aromatase at 20 μM and embryo malformations. Others also published studies on the endocrine disrupting potency (Kim et al., 2008).

2.4.1.3 Genotoxic substance

Amer et al. (2003) shows sperm head abnormalities at 50 mg/kg. McCarroll et al. (2002) reports liver tumors in mice.

2.4.1.4 Effects on the environment

Carbendazim can be harmful to fish or other aquatic life and it is so strongly adsorbed on soil organic matter. The half-life of carbendazim in soil from about 3 days to 12 months, depending on soil type. Examples, the half-life of 6-12 months on bare soil and 3-6 months on turf and is mainly decomposed by microorganisms. It has a low acute toxicity for birds and is not toxic to bees and the half-life of carbendazim on the environment is shown in Table 2.2.

Table 2.2 Half-life of cabendazim

Fungicides	**Condition systems**						
	Air	Soil Types				Water	Plant
Carbendazim		silty sand	loam	clay loam	loamy sand		
	<0.27 day	32 days	9 days	8 days	22 days	60 days	14 days

Source: The Joint FAO/WHO Meeting on Pesticide Residues (JMPR), 1998.

2.4.2 Analysis of carbendazim residues

Over the years, research in the fields of carbendazim residue analysis in food has experienced a continuous expansion of the number of techniques available for determining their content in different fruits and vegetables. The usual determination methods are resource consuming to quantify the residues at trace levels. It is a tendency to develop a high sensitive sample and low cost analysis method (Taylor et al., 2002).

The most commonly used analytical method for the analysis of carbendazim is liquid chromatography with UV (Al-Ebaisat et al., 2011; Veneziano et al., 2004), diode-array (Michel and Buszewski, 2004), fluorescence (Wu et al., 2009; Hu et al., 2004) or mass spectrometric detections (Blasco et al., 2006). Different extraction solvents include acetone (Nemeth-Konda et al., 2002), acetonitrile (Romero-Gonzalez et al., 2008), methanol (Veneziano et al., 2004), ethyl acetate (Blasco et al., 2006; Pan et al., 2008)], dichloromethane (Hiemstra et al., 2007), followed by homogenizing, then shaking by using sonication (Pan et al., 2008). Solid-phase extraction (SPE), using C18 bonded silica procedure, employed for isolation (Juan-Garcia et al., 2007). Pan et al. (2008) reported that HPLC condition was required mobile phase modifiers such as methanol-water or acetonitrile-water to improve the peak shape and/or resolution and the application of sorption of interferences on SAX/PSA dual-layer solid phase extraction was impressive. Several methods can be found in the literature for the analysis of carbendazim in fruits, vegetables, water, soils and wine samples (Lesueur et al., 2008; Pan et al., 2008; Singh et al., 2007; Blasco et al., 2006; Nozal et al., 2005; Zamora et al., 2003).

Carbendazim residues in fruits and vegetables, it was found in 40-50% of analysed strawberries, citus fruits, champingnons, mangoes, and stone fruits (Anastassiades et al., 1998) and 51.9% of oranges and tangerines in the concentrateCarbendazim residues in fruits and vegetables, it was found in 40-50% of analysed strawberries, citus fruits, champingnons, mangoes, and stone fruits (Anastassiades et al., 1998) and 51.9% of oranges and tangerines were obtained in determining carbendazim residue in the concentration range of 0.02-0.04 mg/kg (Blasco et al., 2006) and 10% of banana samples were found at concentration ranging from 0.140-1.100 mg/kg (Veneziano et al., 2004).

2.4.3 Maximum residue limits of carbendazim

Pesticide residues on crops are monitored through the use of Maximum Residue Limits (MRL), which are based on the analysis of the quantity of a given pesticide remaining on fruit and vegetable samples. The MRL is usually determined by repeated of field trials, where the crop has been treated according to good agricultural practice (GAP) and an appropriate pre harvest interval or withholding period has elapsed. MRLs of carbendazim for Australia, Codex, EU, Spain, and Thailand in some vegetables is shown Table 2.3.

Table 2.3 Maximum residue limits (MRLs) of carbendazim

Plants	MRLs (mg/kg)				
	Australia	Codex	EU	Spain	Thailand
Cauliflower	-	-	0.1	-	-
Cucumber	-	0.05	1.0	2.0	-
Ginger root	10.0	-	-	-	-
Kale	-	-	0.1	-	-
Pepper	-	2.0	-	2.0	2.0
Tomato	-	0.5	0.5	2.0	0.5

Source: The Australian Pesticides and Veterinary Medicines Authority, 2011; European Commission, 2011; Thai Agricultural Commodity and Food Standard TACFS 9002, 2008; Codex Alimentarius, 2006; WHO, 1993.

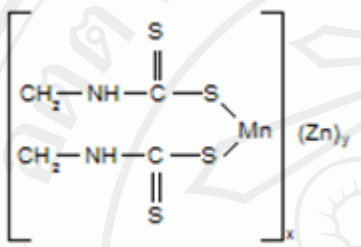
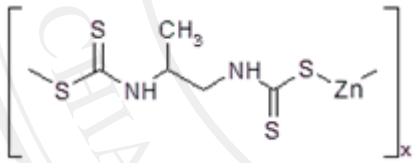
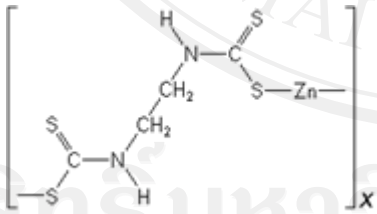
2.5 Mancozeb

Dithiocabamates (DTCs) are important organosulfur compounds and their wide use fungicides for protection of crops, fruits, vegetables, seed, and ornamental plants. DTCs are polymeric complexes with transition metals, such as manganese in maneb, zinc in zineb and propineb, manganese and zinc in mancozeb. The DTCs can be subdivided into three classes: (1) dimethyldithiocarbamates including ziram, ferbam and thiram; (2) ethylenebis (dithiocarbamates) including maneb, zineb, nabam, metiram and mancozeb; and (3) propylenebis (dithiocarbamates) including propineb (Schmidt et al., 2013). DTCs can decompose or metabolize to carbon disulfide (CS_2) and ethylenethiourea (ETU) (Choua et al., 2004; Shukla and Arora 2001). In Thailand, the most imported DTCs including mancozeb, propineb and zineb (Table

2.4) between 2007 and 2012 (DOA, 2013). Most of the DTCs are applied as fungicides and some are classified by the World Health Organization as being hazardous (WHO, 2005). Dithiocarbamate can result in neuropathology, thyroid toxicity and developmental toxicity in chronically exposed (Caldas et al., 2011)

Mancozeb, a [[1,2-etilenbisditiocarbamate](2-)] of manganese and zinc mixture, is a synthetic pesticide and it is used to protect many fruit, vegetable, nut and field crops against a wide spectrum of fungal diseases, including potato blight, leaf spot, scab, and rust. It is also used for fruits and vegetables, such as cucurbits, banana, papaya, potato, onion, garlic, tomatoes, herb, okra, lettuce. Mancozeb is available as dusts, liquids, water dispersible granules, as wettable powders, and as ready-to-use formulations.

Table 2.4 Structure and quantity of imported dithiocarbamates in Thailand

Structure of dithiocarbamates	Quantity of imported dithiocarbamates in Thailand (Tons)					
	2007	2008	2009	2010	2011	2012
Mancozeb (MW = 541.0) 	2,249	2,143	1,192	1,829	1,719	1,405
Propineb (MW = 289.8) 	647	890	665	674	644	733
Zineb (MW = 275.75) 	184	152	64	104	111	3

Source: The Department of Agriculture (DOA), Thailand.

2.5.1 Toxicity of mancozeb

Mancozeb is effective against a wide range of foliar fungal diseases. It is known to disrupt the respiratory activity of the target fungi. It is a practically nontoxic ethylene bisdithiocarbamate in EPA toxicity class IV (practically nontoxic).

2.5.1.1 Acute toxicity

Mancozeb has a very low acute toxicity to mammals and it is practially nontoxic via the oral route with reported oral LD_{50} of greater than 5000 mg/kg to greater than 11,200 mg/kg in rats. Via the dermal route it is practically nontoxic as well, with reported dermal LD_{50} values of greater than 10,000 mg/kg in rats, and greater than 5000 mg/kg in rabbits. It is a mild skin irritant and sensitizer, and a mild to moderate eye irritant in rabbits. Workers with occupational exposure to mancozeb have developed sensitization rashes.

2.5.1.2 Chronic toxicity

No toxicological effects were apparent in rats fed dietary doses of 5 mg/kg/day in a long-term study. Impaired thyroid function was observed as lower iodine uptake after 24 months in dogs fed doses of 2.5 and 25 mg/kg/day of mancozeb, but not in those dogs fed 0.625 mg/kg/day. A major toxicological concern in situations of chronic exposure is the generation of ethylenethiourea (ETU) in the course of mancozeb metabolism, and as a contaminant in mancozeb production. ETU may also be produced when EBDCs are used on stored produce, or during cooking. In addition to having the potential to cause goiter, a condition in which the thyroid gland is enlarged, this metabolite has produced birth defects and cancer in experimental animals.

2.5.1.3 Reproductive effects

In a three-generation rat study with mancozeb at a dietary level of 50 mg/kg/day there was reduced fertility but no indication of embryotoxic effects. In another study in which pregnant rats were exposed to mancozeb by inhalation, toxic effects on the pups were observed only at exposure levels (55 mg/m3) that were also toxic to the dams. It is unlikely that mancozeb will produce reproductive effects in humans under normal circumstances.

2.5.1.4 Teratogenic effects

No teratogenic effects were observed in a three-generation rat study with mancozeb at a dietary level of 50 mg/kg/day. Developmental abnormalities of the body wall, central nervous system, eye, ear, and musculoskeletal system were observed in experimental rats which were given a very high dose of 1320 mg/kg of mancozeb on the 11th day of pregnancy. Mancozeb was not teratogenic to rats when it was inhaled by pregnant females at airborne concentrations of 0.017 mg/L. In pregnant rats fed 5 mg/kg/day, the lowest dose tested, developmental toxicity was observed in the form of delayed hardening of the bones of the skull in offspring. In view of the conflicting evidence, the teratogenicity of mancozeb is not known.

2.5.1.5 Mutagenic effects

Mancozeb was found to be mutagenic in one set of tests, while in another it did not cause mutations. Mancozeb is thought to be similar to maneb, which was not mutagenic in the Ames Test. Data regarding the mutagenicity are inconclusive but suggest that mancozeb is either not mutagenic or weakly mutagenic.

2.5.1.6 Carcinogenic effects

No data are available regarding the carcinogenic effects of mancozeb. While studies of other EBDCs indicate they are not carcinogenic, ETU (a mancozeb metabolite), has caused cancer in experimental animals at high doses. Thus, the carcinogenic potential of mancozeb is not currently known.

2.5.1.7 Organ toxicity

The main target organ of mancozeb is the thyroid gland; the effects may be due to the metabolite ETU.

2.5.1.8 Effects on the environment

Mancozeb is slightly toxic to birds on an acute basis. The lethal concentration fifty (LC_{50}) is the concentration of a material in air or water that kills half of a population that is experimentally exposed to the chemical for a given time period. The EPA is currently reviewing data on the effects of mancozeb on bird reproduction and aquatic organisms but not hazardous to honey bees. The breakdown of mancozeb in soil is four to eight weeks under normal field conditions and degrades in water with a half-life of one to two days at pH 5, 7 and 9. The half-life of mancozeb and ETU on the environment is shown in Table 2.5.

Table 2.5 Half-life of mancozeb and ETU

Fungicides	Condition systems			
	Air	Soil	Water	Plant
Mancozeb	-	4-8 weeks	1-2 days	15 days
ETU	8-9 days	1-7 days	1-4 days	1-7 days

Source: EXTOXNET, 1996, California.

2.5.2 Analysis of mancozeb residues

DTCs can decompose or metabolize to carbon disulfide (CS_2) and DTCs residues (i.e. mancozeb, propineb, and zineb) have also been determined in fruits and vegetables using gas and liquid chromatographic methods. Various methods for the analysis of DTC residues on fruits and vegetables, the most used gas chromatography (GC) (Kazos et al., 2007; Cesnik and Gregoric, 2006), high performance liquid chromatography (HPLC) (Kazos et al., 2007) and spectrophotometric (Caldas et al., 2001). And analysis of CS_2 evolved during acidic treatment of DTC residues (Cesnik and Gregoric, 2006). For examples, Vryzas et al. (2002) determined residues of ethylenebis(dithiocarbamate) (i.e. maneb, zineb, and mancozeb) and N,N-dimethyldithiocarbamate (i.c. thiram and ziram) fungicides in dry tobacco leaves and peaches. The residues were extracted and hydrolyzed to CS_2 in a single step using microwave energy in a closed-vessel system while the evolved CS_2 was trapped in a layer of iso-octane which then was taken for gas chromatographic−flame photometric (GC-FPD) analysis. This combined extraction−hydrolysis step was carried out in 10 and 15 min for sets of 12 samples of tobacco and peach matrices, respectively. Total sample preparation time for GC analysis was 40 min. The limits of detection (LOD) were 0.005 mg/kg for thiram and ziram on peaches and 0.1 mg/kg for maneb, zineb, and mancozeb on tobacco. The respective LOD and limit of quantitation(LOQ) levels in CS_2 equivalents were 0.003 and 0.006 mg/kg on peaches and 0.04 and 0.2 mg/kg on tobacco, respectively. Recoveries in the 0.01−60 mg/kg spiking range were 80−100% with respective relative standard deviations <20%. The method was used in detecting more than commercial tobacco samples also including various cigarette brands

(Vryzas et al., 2002). Coldwel et al. (2003) reported the determination of DTCs in occupational hygiene sampling devices which consisting of glass fiber (GF/A) filters, cotton pads, cotton gloves and disposable overalls, were reduced under acidic conditions and the CS_2 evolved as a decomposited product was extracted into isooctane. The isooctane was then analyzed using gas chromatography with mass spectrometry (GC-MS) to detect CS_2 which provided a quantitative result of the DTCs. Recoveries obtained were generally within a 70–110% range and reproducibility was typically better than 15% RSD (Coldwell et al., 2003).

Moreover, Marosanovic and Pandurevic (2010) determined the DTCs in fruits and vegetables (plum, cherry, raspberry, strawberry, blackberry, grape, apple, cabbage, cucumber, tomato, etc.) in Serbia by gas chromatograph with electron-capture detector and head-space technic. Validation of the method was performed in two ways, spiked samples with CS_2 and thiram. The recovery of this method was 76-85% (72-80% for thiram, 79-85% for CS2). LOQ of DTCs was 0.05 mg/kg. Six samples were determined and the DTCs' concentration was 0.13 - 1.1 mg/kg. More than 95% of analyzed samples from Serbian markets contained no DTCs.

The analysis of DTCs in apples, pears, plums, table grapes, papaya and broccoli was found at concentrations ranging from 0.03 mg/kg to 2.69 mg/kg expressed as the equivalent amount of CS_2. None of the values exceeded the Maximum residue level (MRL) set by the European Union (Schmidt et al., 2013). In Brazil, the local market of the Federal District, detectable levels were found in 60.8% of the samples (520 food samples including papaya, banana, apple, strawberry, orange, potato, tomato, rice and dry beans) with the highest levels (up to 3.8 mg/kg) found in strawberry, papaya and banana. No residues were found in rice (polished) and only one dry bean

sample had detectable levels of the fungicides. Detectable residues were found in the pulp of banana, papaya (including the seeds) and orange (50–62% of the analyzed samples) (Caldas et al., 2004). The method involves a selective reaction combined with liquid phase microextraction (LPME) and transmission infrared measurements. The usefulness of the methodology has been evidenced by the determination of mancozeb residues in strawberries, lettuce and corn samples at concentrations between 1 and 5 mg/kg.

2.5.3 Maximum residue limits of mancozeb

The MRLs of mancozeb for cucumber, ginger, pepper, and tomato set in Codex, Japane, and Thailand is shown Table 2.6.

Table 2.6 Maximum residue limits (MRLs) of mancozeb

Plants	**MRLs (mg/kg)**		
	Codex	Japan	Thailand
Cucumber	2.0	2.0	2.0
Ginger root	-	0.2	-
Pepper	10.0	-	2.0
Tomato	-	5.0	2.0

Source: Thai Agricultural Commodity and Food Standard TACFS 9002, 2008; Codex Alimentarius, 2006; Japan Ministry of Health, Labor and Welfare (JMHLW), 2006.

2.6 Health risk assessments

A health risk assessment is the process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future. It is a process intended to estimate the risk to a given target organism, system or (sub) population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The risk assessment process includes four additional steps: 1) hazard identification, 2) hazard characterization or dose-response assessment, 3) exposure assessment and 4) risk characterization. The risk assessment paradigm is summarized in Table 2.7 (IPCS, 2004).

Table 2.7 Paradigm for risk assessment, including problem formulation

Step	Description	Content
1. Hazard identification	Identifies the type and nature of adverse health effects	- Human studies - Animal-based toxicology studies - In vitro toxicology studies - Structure–activity studies
2. Hazard characterization or Dose-response assessment	Qualitative or quantitative description of inherent properties of an agent having the potential to cause adverse health effects	- Selection of critical data set - Modes/mechanisms of action - Kinetic variability - Dynamic variability - Dose–response for critical effect

Table 2.7 Paradigm for risk assessment, including problem formulation (Continued)

Step	Description	Content
3. Exposure assessment	Evaluation of concentration or amount of a particular agent that reaches a target population	- Magnitude - Frequency - Duration - Route - Extent
4. Risk characterization	Advice for decision-making	- Probability of occurrence - Severity - Given population - Attendant uncertainties

Source: IPCS, 2004.

Health risk assessments of chemicals can be performed to evaluate past, current and even future exposures to any chemical found in air, soil, water, food, consumer products or other materials. They can be quantitative or qualitative in nature. Risk assessments are often limited by a lack of complete information. To be protective of public health, risk assessments are typically performed in a manner that is unlikely to underestimate the actual risk. Regardless, chemical risk assessments rely on scientific understanding of pollutant behavior, exposure, dose and toxicity. The risk assessment paradigm is presented four additional steps: 1) hazard identification, 2) dose-response assessment, 3) exposure assessment and 4) risk characterization (Figure 2.6).

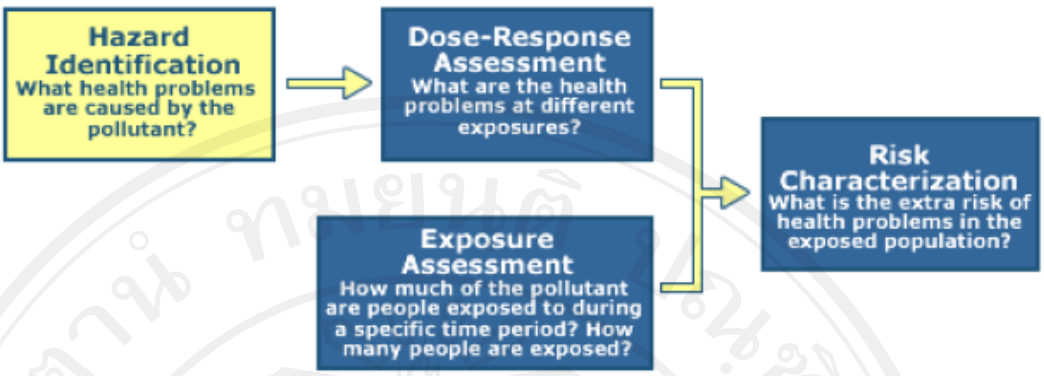


Figure 2.6 The four step of risk assessment process of chemicals

Source: Burpee, 2006.

2.6.1 Hazard identification

Hazard identification is generally the first step in a risk assessment and is the process used to identify the specific chemical hazard and to determine whether exposure to this chemical has the potential to harm human health. For the purposes of hazard identification involves establishing the identity of the chemical of interest and determining whether the chemical has been considered hazardous by organizations.

2.6.1.1 Chemical identity

Given sufficient time and resources, the surest way for potentially hazardous chemicals to be identified is sample collection and chemical analysis. Collection and analysis of samples, however, generally require preliminary identification of the chemical of interest, as the appropriate collection and laboratory analysis method will depend on the specific chemical. Thus, even when chemical analyses are planned, some preliminary identification of the chemical is needed. In cases where chemical analyses are not possible, this preliminary identification may comprise the entire hazard identification step.

Chemicals and their hazards can be identified from a number of internal and external sources. Internal sources include company documents and people who work with the chemical for example, a plant manager or operator. Generally, in cases where the source of the chemical is easily identified, the chemical is listed as an ingredient on the chemical packaging, on the associated chemical safety card or material safety data sheet or on a list of chemicals used in the industrial process. The same identification materials can be relied upon for cases in which the chemicals of concern come from multiple sources; however, this identification may also involve additional determinations of whether any identified chemicals will behave differently or will form different chemicals when mixed together. If the identity of the chemical is not known, the assessor should gather information from various resources and infer the types of chemicals of concern.

2.6.1.2 Hazardous properties

Once identified, the potential hazard of the chemical can be determined from the available scientific data on the chemical, generally data from toxicological or epidemiological studies. A chemical may be associated with one or more hazards to human health. Several schemes for classification of hazard information have been developed. In general, chemicals are classified according to health hazards that they pose, such as neurological, developmental, reproductive, respiratory, cardiovascular and carcinogenic effects.

The weight of evidence for carcinogenic effects of a chemical in humans is another important feature of hazard identification. The International Agency for Research on Cancer (IARC) categorizes chemicals and other agents into one of five

categories based on the strength of evidence that an agent could alter the age-specific incidence of cancer in humans:

Group 1 : the agent is carcinogenic to humans

Group 2A : the agent is probably carcinogenic to humans

Group 2B : the agent is possibly carcinogenic to humans

Group 3 : the agent is not classifiable as to its carcinogenicity to humans

Group 4 : the agent is probably not carcinogenic to humans

A cancer hazard in the context of the IARC classification system is an agent that is capable of causing cancer under some circumstances. A thorough description of the IARC cancer hazard classifications and other fundamental aspects of the assessment objectives and methods of IARC can be found in the preamble that is included in each monograph published by the agency (IARC, 2006).

2.6.2 Dose-response assessment

A dose-response relationship describes how the likelihood and severity of adverse health effects (the responses) are related to the amount and condition of exposure to an agent (the dose provided). Although this webpage refers to the “dose-response” relationship, the same principles generally apply for studies where the exposure is to a concentration of the agent (e.g., airborne concentrations applied in inhalation exposure studies), and the resulting information is referred to as the "concentration-response" relationship. The term “exposure-response” relationship may be used to describe either a dose-response or a concentration-response, or other specific exposure conditions.

Typically, as the dose increases, the measured response also increases. At low doses there may be no response. At some level of dose the responses begin to occur in a small fraction of the study population or at a low probability rate. Both the dose at which response begin to appear and the rate at which it increases given increasing dose can be variable between different pollutants, individuals, exposure routes, etc.

The shape of the dose-response relationship depends on the agent, the kind of response (tumor, incidence of disease, death, etc.), and the experimental subject (human, animal) in question. For example, there may be one relationship for a response such as 'weight loss' and a different relationship for another response such as 'death'. Since it is impractical to study all possible relationships for all possible responses, toxicity research typically focuses on testing for a limited number of adverse effects. Upon considering all available studies, the response (adverse effect), or a measure of response that leads to an adverse effect (known as a 'precursor' to the effect), that occurs at the lowest dose is selected as the critical effect for risk assessment. The underlying assumption is that if the critical effect is prevented from occurring, then no other effects of concern will occur.

As with hazard identification, there is frequently a lack of dose-response data available for human subjects. When data are available, they often cover only a portion of the possible range of the dose-response relationship, in which case some extrapolation must be done in order to extrapolate to dose levels that are lower than the range of data obtained from scientific studies. Also, as with hazard identification, animal studies are frequently done to augment the available data. Studies using animal subjects permit the use of study design to control the number and composition (age, gender, species) of test subjects, the levels of dose tested, and the measurement of

specific responses. Use of a designed study typically leads to more meaningful statistical conclusions than does an uncontrolled observational study were additional confounding factors must also be considered for their impact on the conclusions. However, dose-response relationships observed from animal studies are often at much higher doses that would be anticipated for humans, so must be extrapolated to lower doses, and animal studies must also be extrapolated from that animal species to humans in order to predict the relationship for humans. These extrapolations, among others, introduce uncertainty into the dose-response analysis.

Dose-response assessment is a two-step process. The first step is an assessment of all data that are available or can be gathered through experiments, in order to document the dose-response relationship(s) over the range of observed doses (i.e., the doses that are reported in the data collected). However, frequently this range of observation may not include sufficient data to identify a dose where the adverse effect is not observed (i.e., the dose that is low enough to prevent the effect) in the human population. The second step consists of extrapolation to estimate the risk (probably of adverse effect) beyond the lower range of available observed data in order to make inferences about the critical region where the dose level begins to cause the adverse effect in the human population.

2.6.2.1 Basic dose-response calculations and concepts

As a component of the first step of the process discussed above, the scientific information is evaluated for a better biological understanding of how each type of toxicity or response (adverse effect) occurs; the understanding of how the toxicity is caused; is called the "mode of action" (which is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding

through operational and anatomical changes, and resulting in the effect, for example, cancer formation). Based on this mode of action, the IARC determines the nature of the extrapolation used in the second step of the process discussed above, either through non-linear or linear dose-response assessment.

2.6.2.2 Non-linear dose-response assessment

Non-linear dose response assessment has its origins in the threshold hypothesis, which holds that a range of exposures from zero to some finite value can be tolerated by the organism with essentially no chance of expression of the toxic effect, and the threshold of toxicity is where the effects (or their precursors) begin to occur. It is often prudent to focus on the most sensitive members of the population; therefore, regulatory efforts are generally made to keep exposures below the population threshold, which is defined as the lowest of the thresholds of the individuals within a population. If the "mode of action" information (discussed above) suggests that the toxicity has a threshold, which is defined as the dose below which no deleterious effect is expected to occur, then type of assessment is referred to by the Agency as a "non-linear" dose-response assessment. The term "nonlinear" is used here in a narrower sense than its usual meaning in the field of mathematics; a nonlinear assessment uses a dose-response relationship whose slope is zero (i.e., no response) at (and perhaps above) a dose of zero.

A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no statistically or biologically significant increases are seen in the frequency or severity of adverse effect between the exposed population and its appropriate control population. In an experiment with several NOAELs, the regulatory focus is normally on the highest one, leading to the common usage of the

term NOAEL as the highest experimentally determined dose without a statistically or biologically significant adverse effect. In cases in which a NOAEL has not been demonstrated experimentally, the term "lowest-observed-adverse-effect level (LOAEL)" is used, which this is the lowest dose tested.

Mathematical modeling, which can incorporate more than one effect level (i.e., evaluates more data than a single NOAEL or LOAEL), is sometimes used to develop an alternative to a NOAEL known as a Benchmark Dose (BMD) or Benchmark Dose Lower-confidence Limit (BMDL). In developing the BMDL, a predetermined change in the response rate of an adverse effect (called the benchmark response or BMR; generally in the range of 1 to 10% depending on the power of a toxicity study) is selected, and the BMDL is a statistical lower confidence limit on the dose that produces the selected response. When the non-linear approach is applied, the LOAEL, NOAEL, or BMDL is used as the point of departure for extrapolation to lower doses.

The reference dose (RfD) is an oral or dermal dose derived from the NOAEL, LOAEL or BMDL by application of generally order-of-magnitude uncertainty factors (UFs). These uncertainty factors take into account the variability and uncertainty that are reflected in possible differences between test animals and humans (generally 10-fold or 10x) and variability within the human population (generally another 10x); the UFs are multiplied together: 10 x 10 = 100x. If a LOAEL is used, another uncertainty factor, generally 10x, is also used. In the absence of key toxicity data (duration or key effects), an extra uncertainty factor(s) may also be employed. Sometimes a partial UF is applied instead of the default value of 10x, and this value can be less than or greater than the default. Often the partial value is ½ log

unit (the square root of 10) or 3.16 (rounded to 3-fold in risk assessment). Note, that when two UFs derived from ½ log units are multiplied together (3 x 3) the result is a 10 (equal to the full UF from which the two partial factors were derived).

Thus, the RfD is determined by use of the following equation 2.1:

RfD = NOAEL (or LOAEL or BMDL) / UFs [2.1]

In general, the RfD is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive groups, such as asthmatics, or life stages, such as children or the elderly) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is generally expressed in units of milligrams per kilogram of bodyweight per day: mg/kg/day.

A similar term, known as reference concentration (RfC), is used to assess inhalation risks, where concentration refers to levels in the air (generally expressed in the units of milligrams agent per cubic meter of air: mg/m3). For more information, please see A Review of the Reference Dose and Reference Concentration Processes.

2.6.2.3 Linear dose-response assessment

If the "mode of action" information (discussed above) suggests that the toxicity does not have a threshold, then this type of assessment is referred to by the Agency as a "linear" dose-response assessment. In the case of carcinogens, if "mode of action" information is insufficient, then linear extrapolation is typically used as the default approach for dose-response assessment (for more detailed information, please see EPA's Guidelines for Carcinogen Risk Assessment). In this type of assessment,

there is theoretically no level of exposure for such a chemical that does not pose a small, but finite, probability of generating a carcinogenic response. The extrapolation phase of this type of assessment does not use UFs; rather, a straight line is drawn from the point of departure for the observed data (typically the BMDL) to the origin (where there is zero dose and zero response). The slope of this straight line, called the slope factor or cancer slope factor, is use to estimate risk at exposure levels that fall along the line. When linear dose-response is used to assess cancer risk, EPA calculates excess lifetime cancer risk (i.e., probability that an individual will contract cancer over a lifetime) resulting from exposure to a contaminant by considering the degree to which individuals were exposed, as compared to the slope factor. Thus,

Cancer Risk = Exposure x Slope Factor **[2.2]**

Total cancer risk is calculated by adding the individual cancer risks for each pollutant in each pathway of concern (i.e., inhalation, ingestion, and dermal absorption), then summing the risk for all pathways.

2.6.3 Exposure assessment

Exposure assessment is used to determine whether people are in contact with a potentially hazardous chemical and, if so, to how much, by what route, through what media and for how long. Because hazard characterization and risk characterization are dependent upon the route (oral, inhalation, dermal) and duration (short-term, medium-term, long-term) of exposure, knowledge of how and when people may be exposed is relevant to the determination of an appropriate guidance or guideline value. When

combined with information on hazard characterization or a guidance or guideline value, exposure information is used to characterize health risks.

The exposure concentration is the concentration of a chemical in a medium with which a person is in contact. These media include air, water and soil in outdoor and indoor locations frequented by a population. Other media include food and consumer products with which people come in contact. Ideally, exposure concentrations will be obtained for media, locations and durations that are representative of potential human contact with a chemical of concern.

2.6.3.1 Routes and pathways of exposure

The medium of exposure refers to air, water, soil, food or products (consumer, commercial or industrial) that are thought to contain the chemical of interest (Figure 2.7). These exposures may occur in occupational or community (i.e. non-occupational) settings or while using products. Ingestion exposure is associated with chemicals in food, water and soil, both indoors and outdoors. Inhalation exposure requires that chemicals be present in air, although it is important to recognize that chemicals with moderate to high vapour pressures and low solubilities can volatilize from water or soil and then be inhaled. Trichloroethene, an organic solvent, is one example of a chemical that readily volatilizes from potable water. Inhalation can also be an important route of exposure to less volatile chemicals, such as polychlorinated biphenyls, when present at elevated concentrations in soil and other solid substrates. Finally, dermal absorption requires contact between a chemical and skin, which can occur in water, during contact with soil, in the presence of high concentrations in air and during occupational or consumer use.

The scope of an exposure assessment can be narrowed with information about the chemical and its properties, from which the important exposure media and routes can be inferred. For example, health-relevant exposures to some chemicals, such as ozone, occur through only one medium, in this case air. For chemicals that can be found in several media, such as lead, pesticides and chloroform, information about the chemical properties and behaviour can point to environmental media or locations where the highest levels of the chemicals are likely. In addition, this information can suggest relevant pathways and routes of exposure. Pathway of exposure refers to the physical course taken by a chemical as it moves from a source to a point of contact with a person (e.g. through the environment to humans via food). Route of exposure refers to intake through ingestion, inhalation or dermal absorption. The exposure routes may have important implications in the hazard characterization step, as the danger posed by a chemical may differ by route.

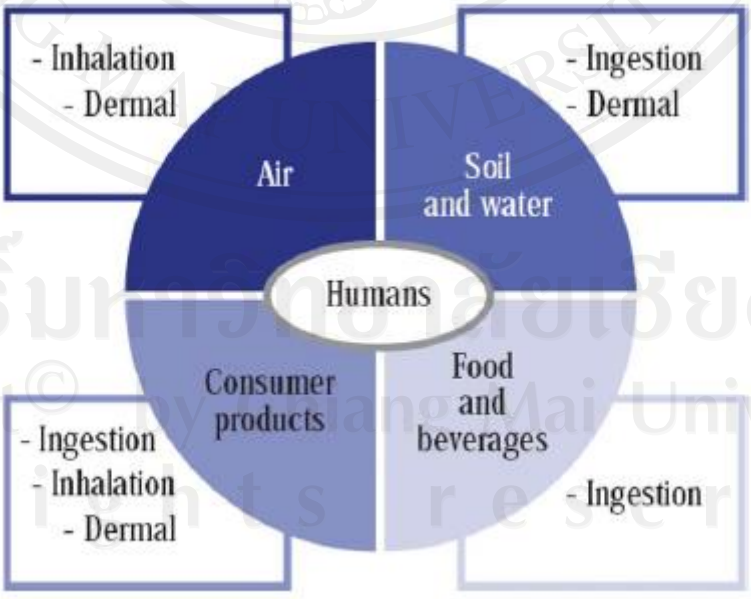


Figure 2.7 Possible exposure media and corresponding means of contact

2.6.3.2 Estimating exposures

While exposure concentrations in personal air and ingested media such as drinking-water should be among the most accurate estimates of actual exposure to a chemical, in practice, they can be difficult, expensive or impractical to determine. In recognition of this limitation, risk assessments, especially screening-level risk assessments, are based upon chemical concentrations in environmental media that are relatively easy to access, such as outdoor air, indoor air, lake water, river water and outdoor soil. These concentrations can be determined from a measurement campaign or a modelling effort.

Exposures can be measured directly, estimated using models or generalized from existing data. Each requires that exposures be determined for time periods relevant to possible adverse health outcomes. For example, if the relevant health hazard is chronic in nature, exposure should be long term as well. Of the three methods, estimating exposures from existing data can often be the simplest approach; however, such data are not often available or entirely relevant to the risk assessment at hand. Measurements, on the other hand, generally provide the most accurate and relevant data, but are the most time and resource intensive, obviating their use for many risk assessments.

2.6.3.3 Duration of exposure

The duration of exposure is a critical element in assessment and estimation of health risks, as the relevant period of exposure is defined by knowledge or theory of the mechanisms of injury or disease. Consequently, the duration of exposure is an explicit component of the design of exposure assessments as well as toxicological studies conducted for purposes of hazard identification and hazard characterization.

Single and short-term exposures over minutes, hours or a day are relevant for chemicals that have an immediate or rapid adverse effect on the body at certain concentrations. Examples of chemicals for which assessment of single and short-term exposure is important include water soluble gases such as sulfur dioxide and asphyxiants such as carbon monoxide.

Medium-term or intermediate exposure is important for chemicals that are thought to exert adverse effects over a period of contact that ranges from weeks to months in duration. Respiratory irritants such as hydrogen sulfide are a class of chemicals for which some public health agencies have developed guidelines for intermediate exposure.

For chemicals that pose a hazard as a result of cumulative or long-term low-dose exposure, long-term average exposures are most relevant for characterization of adverse effects. Chemicals such as polychlorinated biphenyls, which have been associated with learning deficits and diabetes, are in this category. Assessments of cancer risk are a special case of long-term exposure for which lifetime average exposure is generally of interest.

2.6.3.4 Concentration and rate of exposure

In practice, exposures are generally expressed as either a concentration of the chemical in the exposure medium or a rate of contact with a chemical over a specific duration. Therefore, this step of the Toolkit must produce an estimate of exposure that is in the same form as the guidance or guideline value—that is, either a rate or a concentration, respectively.

For example, concentrations in contact media are usually expressed in units of micrograms per cubic metre ($\mu g/m^3$) for air, micrograms per litre ($\mu g/L$) for water

and milligrams per kilogram (mg/kg) for solids such as soil, dust and food. Rate of exposure for a chemical is typically referred to as average daily dose, with units of milligrams of chemical per kilogram of body weight per day (mg/kg body weight per day). In general, exposure rate is calculated as the concentration of a chemical in an exposure medium multiplied by the rate at which a person inhales or ingests that medium, divided by a representative body weight.

As shown in Equation 2.3, the period of exposure and averaging time of exposure are considered explicitly as well:

$$\textbf{Exposure rate} = \frac{\textbf{concentration} \times \textbf{contact rate} \times \textbf{exposure duration}}{\textbf{body weight} \times \textbf{averaging time}} \qquad [2.3]$$

where:

concentration is the amount of chemical per mass or volume of the medium

contact rate is the mass or volume of the medium in contact with the body

exposure duration is the period of time over which the person is in contact with the chemical

body weight is the body weight over the averaging time

averaging time is the period of time over which the exposure is relevant for health risk characterization

The averaging time used in calculation of average daily dose is typically different for estimation of non-cancer and cancer risks. For chemicals that pose a non-cancer hazard, the average exposure during the period of contact with a chemical is generally the relevant duration of exposure for risk assessment. For cancer risk

assessment, however, the averaging time is fixed at a lifetime, which is commonly assumed to be 70 years in risk assessments.

2.6.3.5 Biomarkers of exposure

Besides the above-described traditional exposure assessment, the use of biological markers is another method with which to evaluate human exposure to a chemical. Biological markers of exposure are considered measures of internal dose, whereas exposure describes the contact with a chemical at the boundary between an individual (e.g. skin, mouth or nostrils) and the environment, food or consumer product.

Numerous biological media are available for use in exposure assessment. Selection of sampling media depends on the contaminant of interest, the pattern of exposure, the timing of exposure, the population studied, ease of collection and storage and participant burden. Biological monitoring is frequently considered invasive; however, several media that can be collected in a non-invasive manner are available for exposure assessment. Blood and urine, as well as exhaled breath and saliva, can be used to document recent exposures; past exposure can be evaluated using blood and urine, as well as keratinized tissues (hair and nails), ossified tissue (teeth and bone), adipose tissue and breast milk. Adipose tissue and bone can also represent future sources of internal exposure. Other media available for biomarker studies include faeces, nasal lavage, tears, sputum, semen, cord blood and buccal cells, which can be feasible means for population exposure monitoring.

2.6.4 Risk characterization

The last step of a chemical risk assessment, the risk characterization, is typically a quantitative statement about the estimated exposure relative to the most appropriate health based guidance value, media-specific quality guideline value or another hazard characterization value, such as the cancer slope factor. In general, the risk statement is derived by either comparing the estimated exposure with a guidance or guideline value or calculating the excess lifetime cancer risk associated with the estimated exposure.

The objective of risk characterization is to evaluate the magnitude of risk to human health. The initial assessment of the health risk is done by integrating information on the identified hazard with the estimated or measured exposure and the health status of the workers. When results of medical surveillance and biological monitoring are available, they should be taken into account. The result of this process will be the assessment of both the qualitative aspects of the risk (target organ affected, function alterations, reversibility, etc.) and the quantitative aspects (high, medium, low probability or adverse effect). A practical, simplified scheme of risk characterization is shown in Figure 2.8. The final step is to determine, based on the severity of the adverse effect and its probability to occur, whether the estimated risk is negligible, acceptable or not acceptable. If it is concluded that the risk is negligible or acceptably low, additional control is not indicated, but this conclusion should be verified by health surveillance.

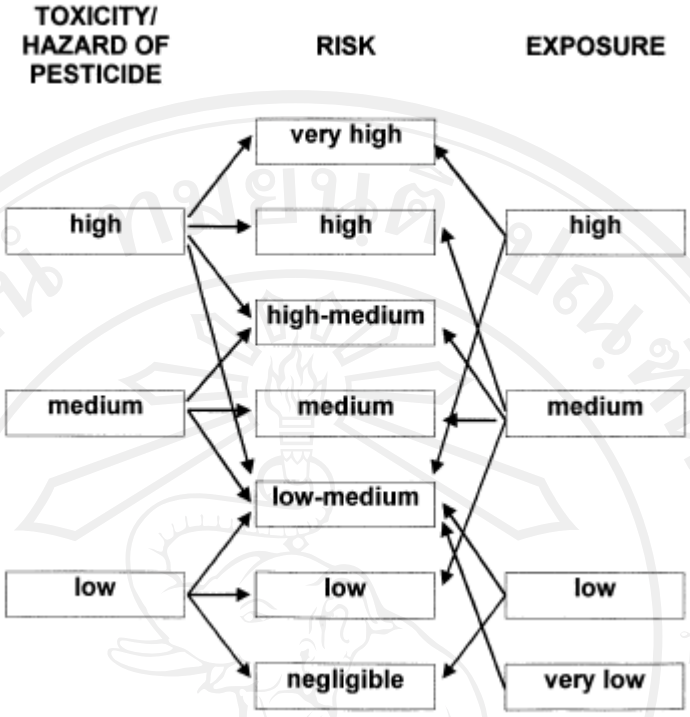


Figure 2.8 Risk characterization

2.6.4.1 Cancer risk

Cancer risk is often expressed as the maximum number of new cases of cancer projected to occur in a population of one million people due. The dose makes the poison even table salt can be toxic in large doses. The exposure to the cancer-causing substance over a 70-year lifetime. For example, a cancer risk of one in one million means that in a population of one million people, not more than one additional person would be expected to develop cancer as the result of the exposure to the substance causing that risk. An individual's actual risk of contracting cancer from exposure to a chemical is often less than the theoretical risk to the entire population calculated in the risk assessment. For example, the risk estimate for a drinking-water contaminant may be based on the health-protective assumption that the individual

drinks two liters of water from a contaminated source daily over a 70-year lifetime. However, an individual's actual exposure to that contaminant would likely be lower due to a shorter time of residence in the area. Moreover, an individual's risk not only depends on the individual's exposure to a specific chemical but also on his or her genetic background (i.e., a family history of certain types of cancer); health; diet; and lifestyle choices, such as smoking or alcohol consumption.

2.6.4.2 Non-cancer risk

Non-cancer risk is usually determined by comparing the actual level of exposure to a chemical to the level of exposure that is not expected to cause any adverse effects, even in the most susceptible people. Levels of exposure at which no adverse health effects are expected are called "health reference levels," and they generally are based on the results of animal studies. However, scientists usually set health reference levels much lower than the levels of exposure that were found to have no adverse effects in the animals tested. This approach helps to ensure that real health risks are not underestimated by adjusting for possible differences in a chemical's effects on laboratory animals and humans; the possibility that some humans, such as children and the elderly, may be particularly sensitive to a chemical; and possible deficiencies in data from the animal studies. Depending on the amount of uncertainty in the data, scientists may set a health reference level 100 to 10,000 times lower than the levels of exposure observed to have no adverse effects in animal studies. Exposures above the health reference level are not necessarily hazardous, but the risk of toxic effects increases as the dose increases. If an assessment determines that human exposure to a chemical exceeds the health reference level, further investigation is warranted.

2.7 The researches for the health risk assessment

Low productivity in agriculture due to damage cause by pests has led to the application of pesticides to control pest infestation. Residues of pesticides applied on crops are often found in the food which can cause chronic effect on the health of humans who consume such products. The aim of this study is to measure pesticides residues in maize and cowpea and compare the values with established safety limits. A total of 37 pesticides comprising 15 organochlorines, 13 organophosphorus and 9 pyrethroids pesticides were identified in maize and cowpea samples obtained from farms in Ejura. Health risk estimation revealed that residues of heptachlor, dieldrin, endrin, b-endosulfna, c-chlordane and chlorfenvinphos found in maize exceeded the Acceptable Daily Intake. Similarly the levels of heptachlor and p,p-DDD found in cowpea also exceeded the acceptable daily intake (Akoto et al., 2013).

Chronic dietary exposure to pesticide residues was assessed for the French population using a total diet study (TDS) to take into account realistic levels in foods as consumed at home (table-ready). Three hundred and twenty-five pesticides and their transformation products, grouped into 283 pesticides according to their residue definition, were sought in 1235 composite samples corresponding to 194 individual food items that cover 90% of the adult and child diet. To make up the composite samples, about 19,000 food products were bought during different seasons from 2007 to 2009 in 36 French cities and prepared according to the food preparation practices recorded in the individual and national consumption survey (INCA2). Dietary intakes were estimated for each subject of INCA2 survey, under two contamination scenarios to handle left-censored data: lower-bound scenario (LB) where undetected results were set to zero, and upper-bound (UB) scenario where undetected results were set to

the detection limit. For 90% of the pesticides, exposure levels were below the acceptable daily intake (ADI) under the two scenarios. Under the lower-bound (LB) scenario, which tends to underestimate exposure levels, only dimethoate intakes exceeded the ADI for high level consumers of cherry (0.6% of children and 0.4% of adults; Nougadere et al., 2012)

Food consumption is one of the key exposure routes of humans to contaminants. This article evaluated the residue levels of 51 pesticides and 16 polychlorinated biphenyls (PCBs) in selected fish and food items which were commonly consumed in the Nantong area of Jiangsu Province, Southeast China. The 51 pesticides and 16 PCBs were analyzed by highly sensitive gas chromatography tandem mass spectrometry (GC-MS/MS). The results suggested that the non-cancer risks of the chemicals investigated can be considered negligible in the Nantong area, however, the cancer risks from lifetime dietary exposure to DDTs and HCB have exceeded the acceptable levels (Wang et al., 2012)

The study ready-to-eat food samples were collected in the production line of the university restaurant of the University of Brasilia, Brazil, which serves non-vegetarian and vegetarian meals daily. Samples were analysed for the presence of ten organophosphorus insecticides (OPs) by GC/FPD. The cumulative acute intake of OPs was estimated using methamidophos and acephate as index compounds (IC). The total cumulative intake represented 9.1% and 47.7% of the methamidophos ARfD for the non-vegetarian and vegetarian diets, respectively. When acephate was used as IC, the total intakes represented 20.7% and 116% of the ARfD for the non-vegetarian and vegetarian diets, respectively. The chronic intake of dithiocarbamates represented 8.6

and 8.9% of the ADI (mancozeb) for the vegetarian and non-vegetarian diets, respectively (Caldasa et al., 2011)

A probabilistic estimation of the exposure of the Brazilian population to the dithiocarbamate pesticides was performed using the Monte Carlo Risk Assessment program (MCRA 3.5). Residue data, as CS_2, for 3,821 samples were obtained from the Brazilian national monitoring program on pesticide residues and from the monitoring program conducted in the Distrito Federal on rice, beans and nine fruits and vegetables. Food consumption data were obtained from a Brazilian household budget survey conducted between 2002 and 2003. Processing factors for washing, peeling or cooking were applied to the residues found in the crops. Daily intakes at the highest percentiles for the general population reached a maximum of 2.0l g CS_2/kg body weight per day (upper band of the 95% confidence interval). Tomato, rice, apple and lettuce were the commodities which contributed most to the intake. Based on the registered uses and the toxicological profile of dithiocarbamates, the risk from exposure was evaluated assuming that all residues came from the use of ethylene-bis-dithiocarbamate (EBDC) or that a fraction of it came from the use of propineb. For this last scenario, a cumulative risk assessment was conducted. In the first scenario, the highest intake reached up to 11.9% EBDC ADI for the general population and up to 31.1% ADI for children. When 30% of the residues were considered as coming from propineb use, the values were 15.2% and 39.7% ADI, respectively (Caldas et al., 2006)

In study of 520 food samples (papaya, banana, apple, strawberry, orange, potato, tomato, rice and dry beans) collected in the local market of the Federal District, Brazil, were analyzed for dithiocarbamate content. An exposure assessment, based on

dithiocarbamate levels detected in the food crops analyzed in this study, confirms that the intake of dithiocarbamates through food consumption in the country does not represent a health risk to consumers, i.e., the estimated daily intake is less than the acceptable daily intake. (Caldas et al., 2004)