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# Biomonitoring of Contemporary Pesticides: Ethylenethiourea in Occupational Settings

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## 1. Introduction

Ethylenebisdithiocarbamates (EBDCs) are widely used fungicides in agriculture because of their efficacy and broad spectrum of antifungal activity. They are mainly used on fruits, ornamental plants, and vegetables (Maroni et al., 2000). EBDCs are salts of the dithiocarbamates; the salts of manganese, zinc or manganese, and zinc are the commercial products known as maneb, zineb, metiram and mancozeb (Figure 1) (Houeto et al., 1995). In dilute suspensions the compounds are not particularly stable, yielding a number of degradation products (Somerville, 1986). Ethylenethiourea (ETU, Figure 1) is present as an impurity in several EBDCs formulations, and it is formed in the presence of moisture and oxygen (Bontoyan et al., 1972; Bontoyan & Looker, 1973). ETU is important in the assessment of human health from exposure to EBDCs because it is the purported source of toxicity from EBDCs (Houeto et al., 1995) and it is a metabolic product of EBDC in mammals, plants, and other organisms (WHO, 1988). Therefore, ETU can be measured in people to assess their exposure to EBDCs.

### 1.1 Exposure assessment using biomonitoring

There are various methods to assess human exposure to EBDCs, such as questionnaires and environmental sampling. One approach that has attracted increased interest in recent years is biomonitoring. Biomonitoring determines a person's internal dose of a chemical by measuring the amount of the chemical or its metabolites in human tissues or fluids (e.g., blood, urine).

Biomonitoring is a powerful tool in assessing exposure to pesticides because such information can accurately and precisely identify people with significant levels of exposure to these chemicals. With this information the prevalence of exposure, the types of jobs that are most hazardous in terms of exposure and at-risk population groups can be identified. In addition, knowing the concentration of the chemical in the blood or urine can assist in the assessment of health risk from the exposure to chemicals that are known to cause disease or disorder, assist in determining the need for immediate interventions to prevent further exposure in the population, and assist in the monitoring the effectiveness of preventive measures. Biomonitoring of pesticides in occupational settings has become increasingly important in the assessment of health risk and it has become an integral part of the overall occupational health and safety strategy. Thus, biomonitoring can be used in exposure assessment and risk assessment based on known health outcomes.

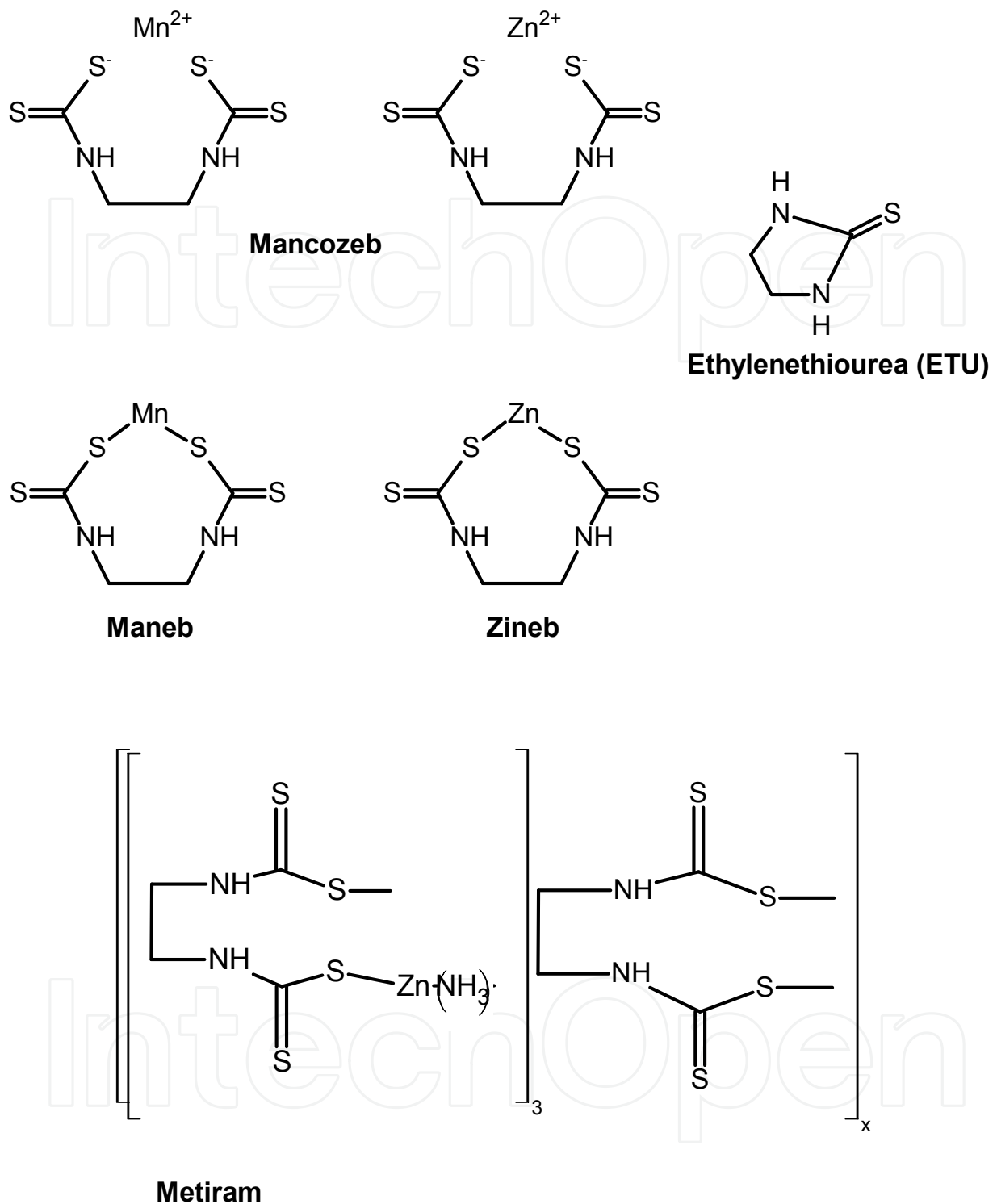


Fig. 1. Structures of the EBDCs Mancozeb, Maneb, Zineb, and Metiran and their metabolite ETU.

### 1.2 Populations at-risk for exposure

Farmers generally use large amounts of agrochemicals, including fertilizers and pesticides, for crop protection in order to enhance agricultural production and efficiency. For farm workers, pesticide exposure is a constant risk because of inappropriate handling of

pesticides, improper use of personal protective equipment and, also, because of inadequate information about the toxicity of the chemicals with which they are working. The improper handling of some of these chemicals without protective equipment and without using appropriate application procedures exposes farm workers to potential health effects from these chemicals. Occupational exposure to pesticides can occur in the field or in greenhouses from the direct handling of pesticides, such as in mixing or loading and during application. Workers who bring in the harvest or clean and maintain the agricultural equipment can be exposed as well. Other workers at risk for exposure to these chemicals include those who manufacture the pesticides.

Although many of the most toxic pesticides have been removed from the market or their use has been restricted in developed countries, there is still heavy use of pesticides without surveillance around the world. Doubts and uncertainties exist concerning the long-term health effects from the chronic or prolonged low-dose exposure to these newer or contemporary pesticides because of inadequate exposure and risk assessments. EBDCs are among these newer classes of pesticides: they have been on the market since the 1940's.

### 1.3 Toxicology

The concern for human health effects from the exposure to EBDCs largely stems from observations made in animal studies. Several long-term studies have been conducted on animals treated with ETU. The prolonged administration of ETU to animals in experimental trials has demonstrated thyroid disorders, including hypertrophy, hyperplasia, and follicular cell tumors, in rats and mice (Ulland et al., 1972; Weisburger et al., 1981; Chhabra et al., 1992; Nebbia & Fink-Gremmels, 1996). In these studies, ETU caused a general decrease in serum thyroxine ( $T_4$ ) levels and increase in serum thyroid-stimulating hormone (TSH) levels, which correlated with morphological changes in the thyroid gland. These hormonal trends are attributed to ETU inhibition of thyroid peroxidase, which is responsible for the incorporation of iodine to thyroglobulin (Marinovich et al., 1997). ETU-induced thyroid tumor is attributed to an imbalance of the thyroid-pituitary axis. Besides the thyroid gland, the major site of ETU-induced carcinogenicity, the liver is also a target. Chronic ETU administration produces hepatocellular carcinoma in mouse and rats (Innes et al., 1969; Belpoggi et al., 2002). However, ETU had mostly negative mutagenic effects in mammalian test systems (Shirasu et al., 1977; Teramoto et al., 1977) and did not induce DNA damage in cultured rat liver cells (Althaus et al., 1982). The International Agency for Research on Cancer (IARC) considers ETU as unclassifiable as a human carcinogen (IARC, 2001). The U.S. National Toxicology Program (NTP) considers ETU as reasonably anticipated being a human carcinogen (NTP, 2004).

Animal studies have demonstrated the ability of Mn-EBDC (maneb), but not manganese or EBDC alone, to selectively disrupt dopaminergic neurons in a manner similar to MPP+ (mitochondrial inhibitor, 1-methyl-4-phenylpyridinium), which can lead to Parkinson's disease (Zhang 2003). Mn-EBDC was shown to increase oxidative stress, decrease proteasomal function, and induce  $\alpha$ -synuclein aggregation with formation of cytoplasmic inclusions in dopaminergic neural cultures (Zhou et al., 2004).

The teratogenic potential of ETU has also been investigated in animal studies. Rats treated before conception to day 15 of gestation with ETU at amounts of 10 mg or more resulted in offspring predominantly with malformation of the brain (Khera, 1973). Another study also investigated the teratogenicity of ETU in rats, mice and hamsters. ETU was teratogenic

when given orally to rats at 20-50 mg/kg body weight per day on day 6 to day 15 of gestation and to hamsters at 270-810 mg/kg body weight per day on days 6 to 13 of gestation (Teramoto et al., 1978). In addition, teratogenic studies were conducted with animals exposed to the EBDCs maneb, zineb and mancozeb. Rats exposed to maneb at a dose of 1420 mg/kg body weight, as a single dose on day 11 of gestation, developed gross malformations in all embryos (Larsson et al., 1976). Mice administered 375, 750 or 1500 mg of maneb/kg body weight on day 7 to 16 of gestation showed a decrease in fetal caudal ossification centers at all dose levels (Chernoff et al., 1979).

#### 1.4 Toxicokinetics

EBDCs can be absorbed through the skin, the mucous membranes, and the respiratory and gastrointestinal tracts (WHO, 1988). Studies of the toxicokinetics and metabolism of EBDCs in laboratory animals have indicated that EBDCs are only partially absorbed, then rapidly metabolized and excreted with no evidence of long-term bioaccumulation (Somerville, 1986). On average, 7.5% of an EBDC dose administered is metabolized to ETU. ETU is predominantly (90%) eliminated in the urine and it has been found to have a half-life of about 28 hours in monkeys, 9 to 10 hours in rats, and 5 hours in mice (Newsome, 1974; Kato et al., 1976; Ruddick et al., 1976; Allen et al., 1978; Rose et al., 1980).

ETU is also a metabolic product of EBDC in mammals, plants, and other organisms (WHO, 1988). Therefore, ETU can be measured in human urine samples collected after EBDC occupational exposure (Kurtio et al., 1990; Colosio et al., 2002). Available data also suggest that in the general population concentrations of ETU in urine can be used as a surrogate parameter for EBDC exposure (Sciarra et al., 1994; Aprea et al., 1996; Aprea et al., 1997; Saieva et al., 2004; Colosio et al., 2002; Colosio et al., 2006).

## 2. Biological monitoring for ETU

Biomonitoring has been used in many exposure studies. The success of a biomonitoring study depends on getting all the parts right: These include overall study design, sample collection, analytical analysis and the interpretation of the resulting data. For biomonitoring EBDCs as well as for other target analytes in urine, the time of sampling and the great variation in the composition of spot urine samples as a result of diurnal variations can influence the results. Considerable knowledge of the toxicokinetics, i.e. the biological processing of a putative toxicant in the body, is essential for defining the time of sampling (Barr et al., 2006). After collection, the samples must be handled carefully to avoid exogenous contamination and degradation due to improper transport and storage.

Studies to evaluate the kinetics of ETU excretion were carried out through the analysis of ETU in urine of exposed workers up to 60 hours from the end of exposure. The highest rate of ETU excretion was around 15 to 22 hours after the end of exposure. Over time the excreted amount decreased, but even after 60 hours from the end of exposure, a small amount of ETU could still be detected in the urine of the exposed workers (Kurtio & Savolainen, 1990). Therefore, for workers exposed to EBDCs the ideal time for sampling is within 16 hours from the end of the work shift because of the rapid metabolism and excretion of metabolites of EBDCs including ETU (Kurtio & Savolainen, 1990; Colosio et al., 2003; Colosio et al., 2007).

Biomonitoring for assessing exposure to environmental chemicals generally requires the measurement of the relevant analytes at much lower concentrations than needed for clinical

chemistry. Specific and sensitive analytical methods are indispensable for assessing exposure in biomonitoring programs. The methods must also be reproducible and rugged. Mass spectrometric analysis, combined with gas chromatography or liquid chromatography, is the analytical method of choice in biomonitoring because of the ability to selectively quantify many environmental chemicals at very low concentrations. Now considerable mass spectrometric analysis is done using the tandem mass spectrometry (MS/MS) technique; MS/MS greatly improves selectivity of the analysis by eliminating potential interferences by other matrix (e.g., urine) components. Also, commonly used to correct for variability in sample extraction is the isotope dilution technique, which involves adding a measured amount of a stable-isotope of the target analyte to the urine sample before extraction. Quantification is done using the ratio of analyte to its isotope.

Several methods have been reported for the measurement of the metabolite ETU in urine. Table I shows the most recent analytical procedures described in the literature. Liquid-liquid extraction (LLE) into dichloromethane seems to be the most commonly used procedure for the extraction of ETU, a highly water-soluble compound. However, usually LLE requires a large volume of organic solvent. Sample preparation is expedited by lyophilizing the urine sample first and then extracting with a much smaller volume of dichloromethane than otherwise would be required. Liquid chromatography (LC), high-performance liquid chromatography (HPLC)-mass spectrometry (MS), or HPLC-MS/MS are the most commonly used analytical methods for the separation and detection of the metabolite ETU. They all use some form of liquid chromatography, but the detection systems range from simple UV or DAD (diode array detector) absorbance detection to sophisticated mass spectrometric analyses as discussed above. Electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) interfaces have shown efficiency in transferring the analyte from the liquid phase as it is eluted from the HPLC column into the gas phase for mass spectrometric analysis. The APCI interface has an advantage over ESI. With ESI, where the ionization occurs in the mobile phase, the sensitivity can be affected by ion suppression due the ionic concentration in the mobile phase itself.

Limits of detection (LOD) and limits of quantification (LOQ) are important parameters that define the limitations of the analytical method. The methods shown in Table I show detection values (LOD or LOQ) that range from 1 µg/L to 0.01 µg/L. It has been suggested that for monitoring the general population, the LOD must be 1 µg/L or less; higher LODs may be adequate for monitoring occupationally exposed workers (Aprea et al., 2002). Because occupationally exposed workers have different levels of exposure depending on the task performed, methods with lower LOD would be preferable if available.

During the method validation procedure it is essential to determine the LOD, LOQ, precision, accuracy of the measurements, extraction recoveries, efficiency of the derivatization reaction (if applicable), linearity, stability of the analyte in the matrix tested, and applicability to the human samples (Barr & Needham, 2002). In addition to comprehensive method validation, quality assurance/quality control (QA/QC) is a very important feature in biological monitoring. QA/QC guarantees the quality of the data by making it possible to detect systematic failures that can occur during the performance of the methods. It has two components: internal quality control, which is a set of procedures used by the staff of a laboratory to continuously confirm the reliability of the results; and external quality assessment, which is a system of checking the laboratory performance by an external agency or institution. The internal quality control programs can include repeat measurements of known biological materials to confirm the validity of an analytical run and



to measure analytical precision, proficiency testing to ensure accuracy as measured against a known reference material, and cross validation to ensure that multiple analysts and instruments obtain similar analytical values (Aprea et al., 2002; Barr & Needham, 2002; Schaller et al., 2002).

### **3. Review of EBDCs exposure studies in occupational settings involving the biomonitoring of the metabolite ETU in urine and its clinical relevance**

#### **3.1 Exposure levels**

Knowledge of exposure levels to EBDCs in occupational settings is an important step in the process of health risk evaluation. The level of the metabolite ETU measured in urine is the most accurate indicator of EBDCs exposure. Only a few studies have been carried out measuring the workers' levels of EBDCs in occupational settings. These studies are outlined in Table II. The assessment of the workers' exposure, based on ETU concentrations in urine, has been done in Mexico in tomato growing areas (Steenland et al., 1997), in areas of floriculture in Ecuador (Colosio et al., 2003), in banana plantations in the Philippines (Panganiban et al., 2004), vineyards in Italy (Colosio et al., 2002; Corsini et al., 2005; Colosio et al., 2007; Fustinoni et al., 2008), in grains, tobacco, vegetable and cut flower areas in Thailand (Panuwet et al., 2007), potato farms in Finland, (Fustinoni et al., 2008), in the flower bulb growing industry in the Netherlands (Fustinoni et al., 2008) and in vegetable growing areas in Bulgaria (Fustinoni et al., 2008). These studies have shown that the concentration of ETU in urine of exposed workers reflects the type of activity on the farm, the use of personal protective equipment such as gloves, respirators, plastic suits and boots, and the level of mechanization and training. In studies in which one of the objectives was to determine the correlation of the type of activity to the degree of exposure, it was shown that EBDCs applicators had higher concentrations of urinary ETU after the end of the work shift than workers engaged in harvesting or maintenance of equipment.

In these EBDCs exposure studies, questionnaires were used in addition to the measurement of ETU in urine. Questionnaires are an important complement to biomonitoring to gain detailed information about the type of work and the working conditions. However, at times, biomonitoring and questionnaire data may not agree. For example, although in these studies the majority of workers reported using personal protective devices, concentrations of urinary ETU were high. Therefore, it is possible that the information reported on the questionnaire did not reflect the reality in the field. Also, in some studies, the control group showed detectable amounts of ETU in the urine. A pilot study conducted in Northern Italy with subjects not occupationally exposed to EBDCs showed that 60% of the subjects had detectable amounts of ETU in urine, with values ranging from 0.5 µg/g creatinine to 11.6 µg/g creatinine (Colosio et al., 2006). In study participants not occupationally exposed, it has been assumed that the presence of ETU results from low-level environmental exposure to EBDCs and ETU, probably by consumption of contaminated food, mainly vegetables, and drinks, such as wine (Aprea et al., 1997).

#### **3.2 Human health effects**

There have been a limited number of epidemiologic studies that investigated the health effects of EBDCs exposure in agricultural workers. Thyroid disorders are a major area of interest based on experimental animal studies demonstrating ETU-induced thyroid gland enlargement

as a consequence of impaired thyroid hormone synthesis and on an occupational health study demonstrating mild but statistically significant lower  $T_4$  concentrations in workers with higher exposure to powdered ETU than those with lower exposure (Smith 1984).

Two cross-sectional studies, with reference groups to control for exposure to EBDCs, have been conducted to investigate the incidence of thyroid gland disorders in agricultural settings (Panganiban et al., 2004; Steenland et al., 1997; Smith 1984). Measures of thyroid hormone levels were carried out among 49 heavily exposed workers without protective equipment spraying EBDCs on tomatoes in Mexico (Steenland et al., 1997). The level of TSH was significantly higher, but within the clinical reference range, in the applicators ( $2.13 \pm 0.15$  mIU/L) compared with the control group ( $1.6 \pm 0.19$  mIU/L). There was no significant difference in  $T_4$  concentrations between these two groups. Studies conducted with banana plantation workers in the Philippines did not find any difference in TSH and  $T_4$  levels between workers and the control group (Panganiban et al., 2004). However, nutritional iodine intake as assessed by urinary iodine concentration was higher in the workers than in the control group. Isolated solitary thyroid nodules were found in 5 workers and 1 control participant. Also, the size of the nodule correlated well with blood ETU concentration (correlation coefficient [ $r^2$ ]=0.956,  $p=0.001$ ) and weakly with urinary iodine concentration ( $r^2=0.759$ ,  $p=0.08$ ), but not with urinary ETU concentration ( $r^2=0.594$ ,  $p=0.213$ ). The significance of the solitary thyroid nodules in this study of agricultural workers remains to be determined through further studies.

Case reports of workers with allergic contact dermatitis (T-cell mediated process) (Nater et al., 1979; Kleibl & Rackova, 1980; Bruze & Fregert, 1983, Campbell & Forsyth, 2003) to EBDCs and ETU have led to several epidemiologic investigations on the potential immunologic effects in workers using or manufacturing EBDCs.

A European-wide study (EUROPIT) was designed to evaluate the immune effects consequent to chronic exposure to EBDCs. This study included five fields in 4 countries: The Netherlands, Italy, Finland and Bulgaria. The total study population consisted of 248 workers exposed to EBDCs and 231 workers serving as controls because of their lack of exposure to EBDCs (Fustinoni et al., 2008; Sterenberg et al., 2008; Van Almelsvoort et al., 2008). The workers completed a self-administered questionnaire and were evaluated for their exposure to EBDCs by detection of ETU in their urine. The urinary ETU concentrations for these comparative groups in this study are shown in Table II (Fustinoni et al., 2008). Immunoglobulin, complement, mitogen-induced cytokines, mitogen-induced proliferative response, and lymphocyte subtypes were used to investigate for alterations in functions of the immune system in these workers. The EUROPIT field study showed no association between exposure to EBDCs and an increased prevalence of allergic contact dermatitis, allergic rhinitis, asthma and asthmatic symptoms, or IgE-mediated allergic response to selected antigens in these workers (Swan et al., 2008; Boers et al., 2008).

An increase in T-cell proliferative response to mitogens (phytohemagglutinin, anti-CD3 monoclonal antibody and phorbol myristate acetate) was observed in workers manufacturing EBDC (mancozeb) compared to controls (Colosio et al., 1996). This cellular response was similarly found in a group of vineyard workers involved in the application of mancozeb (Corsine et al., 2005). In addition, an increase in complement (C3 and C4) and IgG4 levels, and a small but statistically significant decrease in IgA levels were found in exposed workers compared to the controls (Steenberg et al., 2008). When lymphocyte subtypes were analyzed, it was ascertained that there was an increase in CD19 cells (lymphocyte B) and a decrease in the percentage of CD25 cells (cells with IL-2 receptor)



compared to the controls (Corsine et al, 2005). Also, the number of CD8 cells (MHC class I-restricted T cells) was higher in exposed workers than in the control group (Steerenberg et al., 2008). Finally, it was also found that agricultural workers had a reduction in LPS-induced TNF- $\alpha$  (Corsine et al., 2005). Although the significance of these immunological data on the health of workers exposed to EBCDs is uncertain, these findings suggest that the exposure to these fungicides can modulate the immune system. The health consequence of these findings in vulnerable populations, such as agricultural workers with co-morbidities, is unknown and can be a topic for future investigation.

Method	Sample Preparation	Analytical System	Detection Limit
Apra et al., 1993	LLE with dichloromethane	HPLC/DAD	LOQ: 0.5 $\mu\text{g/g}$ creatinine
Debbart & Moore, 2002	LLE with dichloromethane	HPLC/UV detector	LOD: 0.5 $\mu\text{g/L}$
Sottani et al., 2003	LLE with dichloromethane	HPLC/ESI-MS/MS	LOD: 0.5 $\mu\text{g/L}$
Fustimoni et al., 2005	LLE with dichloromethane, BSTFA derivatization	GC/MS	LOD: 0.6 $\mu\text{g/L}$
El Balkhi et al., 2005	SPE with dichloromethane	HPLC/DAD	LOQ: 1 $\mu\text{g/L}$
Montesano et al, 2007	Lyophilization, extraction with dichloromethane	HPLC/APCI MS/MS	LOD: 0.16 $\mu\text{g/L}$
Lindh et al., 2008.	Single-step extraction/PFBBBr derivatization	LC/ESI-MS/MS	LOD: 0.05 $\mu\text{g/L}$
Jones et al., 2010	LLE with dichloromethane	LC/APCI-MS	LOD: 0.25 $\mu\text{g/L}$
Jayatilaka et al., 2010	Lyophilization, 96-well-plate automated extraction with dichloromethane	HPLC/APCI-MS/MS	LOD: 0.01 $\mu\text{g/L}$

Table 1. Methods for measuring the ETU metabolite in urine

The chronic exposure of humans to the EBDC maneb or in combination with the herbicide paraquat has been linked to the neurodegenerative disorder Parkinson's disease, based on epidemiologic studies (Ferraz et al., 1988; Costello et al., 2009) and reports of Parkinsonism in workers exposed to maneb (Ferraz et al., 1988; Meco et al., 1994). Although the toxic effect have been attributed to the manganese present in this pesticide (Barbeau, 1984), an independent contribution of the Mn-EBDC complex to this disorder is plausible (Hoogenraad, 1988; Zhang, 2003). Due the limitations of these and other studies to date focusing on the health effects from the exposure to EBCDs in humans and, also, because some of the observations were subclinical or subtle, it is important to further investigate the clinical significance of occupational exposure to EBCDs.

Reference	Country/Area	Cultivation	Exposed Workers/Tasks and Controls	ETU levels in urine
Steenland et al., 1977	Mexico/Cuernavaca	Tomatoes	Applicators (n=49)	58 ± 26 µg/L <sup>a</sup>
			Landowners (n=14)	12 ± 3 µg/L
			Controls (n=31)	below LOD
Colosio et al., 2002	Italy/Lombardy region	Grape Vine	Workers (n=26)	
			Baseline	0.5 - 3.4 µg/g creatinine <sup>b</sup>
			End of Work Shift	0.5 - 95.2 µg/g creatinine
			Controls (n=13)	< 0.5 µg/g creatinine
Colosio et al., 2003	Ecuador/ around Quito	Flowers	Applicators	1.5 - 34.5 µg/g creatinine <sup>b</sup>
			Harvesting	0.4 - 26.4 µg/g creatinine
			Post-harvesting	0.4 - 11.1 µg/g creatinine
			Maintainers of Equipment	3.2 - 6.5 µg/g creatinine
			Controls	0.4 - 2.1 µg/g creatinine
Panganiban et al., 2004	Philippines	Banana	Directly Exposed Workers <sup>e</sup> (n=57)	378.34 ± 50.11 µg/L <sup>c</sup>
			Indirectly Exposed Workers <sup>f</sup> (n=3)	267.16 ± 69.9 µg/L
			Controls (n=43)	26.31 ± 6.39 µg/L
Corsini et al., 2005	Italy/Northern Italy	Grape Vine	Workers (n=13)	
			Baseline	< 0.5 µg/g creatinine <sup>d</sup>
			End of Work Shift	2.5 µg/g creatinine
Colosio et al., 2007	Italy/Northern Italy	Grape Vine	Workers (n=48)	
			Baseline	1.8 ± 5.3 µg/g creatinine <sup>c</sup>
			End of Work Shift	14.9 ± 13.0 µg/g creatinine
Panuwet et al., 2008	Thailand/Pong Yaeng	Vegetables	Workers (n=67)	13.2 µg/g creatinine <sup>d</sup>
		Flowers		
		Lychees		
	Thailand/Inthakhin	Grains	Workers (n=69)	2.2 µg/g creatinine
		Tobacco		
Fustinoni et al., 2008	Bulgaria	Vegetables	Workers (n=55), Controls (n=45)	49.6 µg/g creatinine, < 0.5 <sup>d</sup>
	Finland	Potatoes	Workers (n=51), Controls (n=51)	7.5 µg/g creatinine, < 0.5
	Italy	Grape Vine	Workers (n=48), Controls (n=45)	11.9 µg/g creatinine, NA
	The Netherlands	Flower Bulbs	Workers (n=42) <sup>g</sup> , Controls (n=40)	0.9 µg/g creatinine, 0.9

<sup>a</sup>Mean ± SE

<sup>b</sup>Range

<sup>c</sup>Mean ± SD

<sup>d</sup>Median

<sup>e</sup>Directly Exposed Workers: Mixers, Applicators, Clean and Maintenance of Equipments.

<sup>f</sup>Indirectly Exposed Workers: Supervisors, Maintenance Crew, Research Aids.

<sup>g</sup>Re-entry Workers.

Table 2. Urinary concentrations of ETU in occupationally exposed workers and control groups.

#### 4. Conclusions

It is clear that EBDCs and in particular the metabolite ETU have important toxic effects in various animal species. It is therefore desirable that further human studies should be done to better assess the exposure to EBDCs and their metabolite ETU through biomonitoring and to define these chemicals potential health risk(s). Much of the general population is potentially exposed to EBDCs, if only through the consumption of fruits and vegetables. For many agricultural workers exposure to EBDCs is chronic. Biological monitoring and the health surveillance of the workers are the basic components for risk assessment and risk management. They determine whether a relation exists between occupational exposure and disease. Unfortunately, biological monitoring and health surveillance are not currently common practices in the field. However, biological monitoring of workers exposed to EBDCs is feasible today because of advances made in analytical laboratory science. Mass spectrometric analytical methods exist that detect ETU – the commonly used marker – in human urine at very low concentrations with excellent accuracy and precision. Although these instruments are expensive and the methods are resource intensive, these concerns will likely lessen in the future because of improved technology.

Until the time when routine assessment in the field becomes feasible, additional exposure studies using biomonitoring should be undertaken to understand better the relation between health effects and levels of exposure. Information from these studies can lead to sound policy and regulatory decisions that will enhance the protection of workers and the environment.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of Centers for Disease Control and Prevention.

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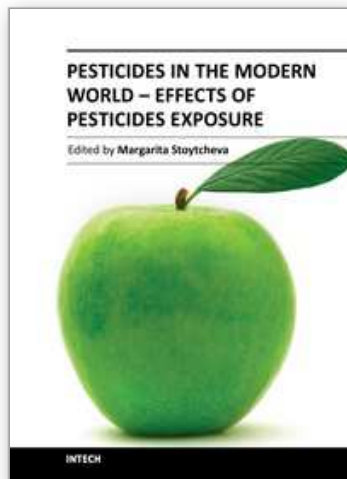
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## **Pesticides in the Modern World - Effects of Pesticides Exposure**

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The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950s marked the beginning of the modern pesticides era and a new stage in the agriculture development. Evolved from the chemicals designed originally as warfare agents, the synthetic pesticides demonstrated a high effectiveness in preventing, destroying or controlling any pest. Therefore, their application in the agriculture practices made it possible enhancing crops and livestock's yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising world's population. Nevertheless, the increase of the pesticide use estimated to 2.5 million tons annually worldwide since 1950., created a number of public and environment concerns. This book, organized in two sections, addresses the various aspects of the pesticides exposure and the related health effects. It offers a large amount of practical information to the professionals interested in pesticides issues.

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