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Dithiocarbamate Toxicity - An Appraisal

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1. Introduction

Dithiocarbamates (DTC) are organosulfur compounds represented by a general structure (R1R2)N-(C=S)-SX, where R can be substituted by an alkyl, alkylene, aryl, or similar other group, and X usually by a metal ion (Edwards, 1991; Kamrin, 1997; US EPA, 2001). Discovered in the 1930s, the DTC were first introduced as fungicides for commercial applications during World War II (Ware & Whitacre, 2004). Besides their wide use as fungicides for treatment of crops, vegetables, seeds, and ornamental plants, they are also used as accelerators in the rubber industry, animal repellants, and biocides in many household products (Edwards et al., 1991; Kamrin, 1997). Figure 1 shows examples of some common DTC pesticides. Thiram, disulfiram, ziram, and ferbam are analogous dialkyl DTC with differences in their R groups and the later two containing different metal ions between their S atoms. Pyrrolidinedithiocarbamate (PDTC) is a monomeric DTC which contains a five member ring attached to its N atom. It is a metabolic inhibitor used in cell physiological studies (Schreck et al., 1992; Cvek and Dvorak, 2007). In ethylene-bis-dithiocarbamates (EBDTC), the R groups of two DTC molecules form an ethylene bridge. The EBDTC are regarded as polymeric DTC because their metal ions can bind several molecules to form polymeric complexes. Some examples of EBDTC are zineb, maneb, and mancozeb which are used in preharvest agricultural applications. The DTC anions are highly reactive which can conjugate with other molecules containing SH groups and form metal chelates. The multisite interactions of DTC give them advantage to influence the biological activities of different proteins, enzymes, and exert toxic effects. Some of those modes of action of DTC compounds have been exploited for their use in clinical applications (Morrison et al., 2010). However, the extensive use of these chemicals in agriculture has raised concern for their effects as occupational and ecotoxicological hazards. Several reviews on the biological and toxicological effects of DTC summarize many studies in the field (Edwards et al., 1991; US EPA, 2001; Cvek and Dvorak, 2007). The objective of this review is to highlight some of the recent findings on the effects of dialkyl DTC and EBDTC with emphasis on studies of the avian system which has not been a focus of earlier literature.

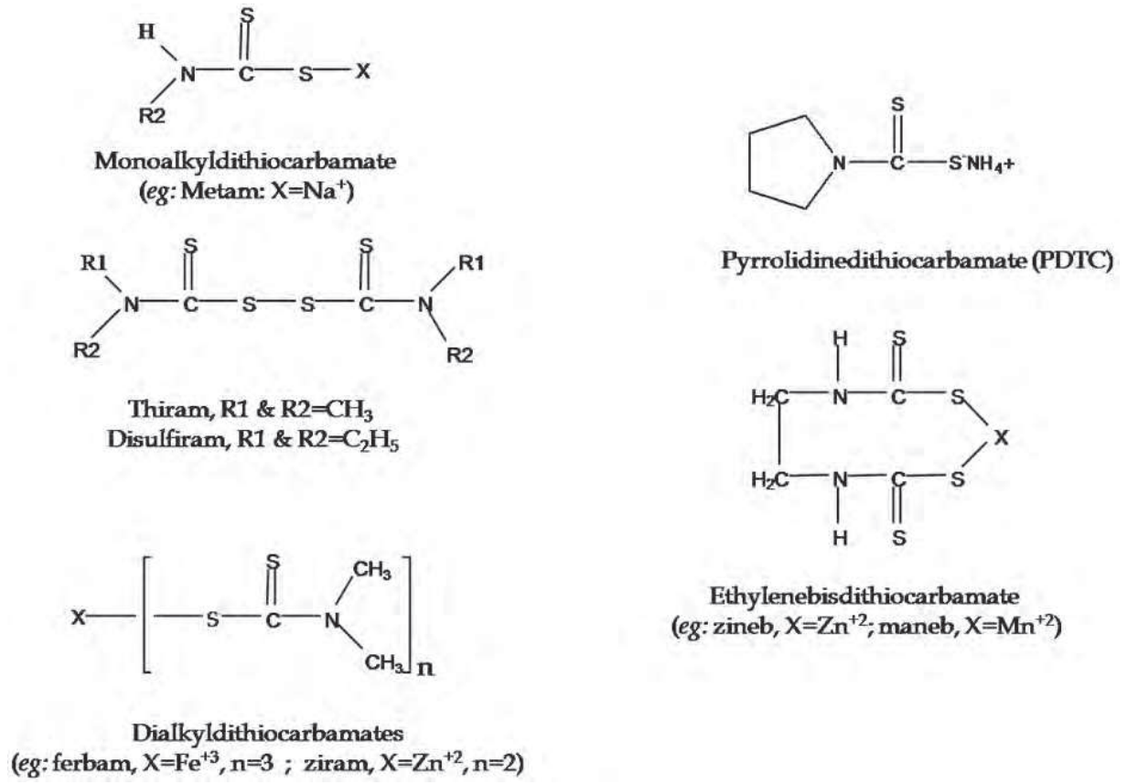

Fig. 1. Structures of some representative dithiocarbamates, R1, R2= alkyl (CH_3, C_2H_5)
X= metal ion (Na^+, Mn^{+2}, Zn^{+2}, Fe^{+3})

2. Metabolism and the toxic effects

The toxicological effects of DTC can occur from their absorption through skin exposure, ingestion, and inhalation. The lipophilic nature of DTC makes them suitable for their passage across the cell membrane. Metabolic studies with representative DTC (ex. thiram, disulfiram, mancozeb) have shown that these chemicals undergo detoxification through S-glucoronidation or biodegrade to different metabolites such as carbon disulfide (CS_2), thiourea, alkylamines, ethyleneamines, and several other biotransformation products (Edwards et al., 1991; US EPA, 2001). CS_2 is a general neuropathic agent and ethylenethiourea (ETU) which is a metabolite of EBDTC, has antithyroid and carcinogenic effects (Edwards et al., 1991; DeCaprio et al., 1992; Houeto et al., 1995; US EPA, 2001). Under physiological conditions most dialkyl DTC can reoxidize to form thiuram disulfide (Burkitt et al., 1998). Thus, the toxic effects of DTC can be due to the whole molecule and their decomposition products such as CS_2 and ETU. The intact DTC molecules exhibit both pro oxidant and antioxidant activities (Nobel et al., 1995; Liu et al., 1996; Orrenius et al., 1996; Burkitt et al., 1998; Wild & Mulcahy, 1999; Cereser et al., 2001). Whereas the disulfide bridges and the metal complexes contribute to their prooxidant effects, the SH contributes to their antioxidant effects (Orrenius et al., 1996; Elskens & Penninckx, 1997). Tissue or organ specific toxic effects of these chemicals may be due to the differential competency of their intracellular passage and binding to crucial structural and functional entities of the cells eventually leading to the metabolic disruptions, pathological changes, and cell death.

3. Molecular and cellular effects

The DTC compounds can form mixed disulfides with other molecules containing SH functions such as proteins, peptides and enzymes modulating their biological activities. The covalent modification of cysteine residues in the active sites can affect enzyme activities. As antioxidants, they react with hydroxyl radicals, peroxides, and superoxide ions, and inhibit their oxidative potential (Nobel et al., 1995; Liu et al., 1996). As prooxidants, DTC increase Cu catalyzed reactive oxygen species (ROS) formation and change the balance of reduced glutathione (GSH) to its oxidized form (GSSG) in favor of the later (Burkitt et al., 1998). GSH is a sulfohydryl containing tripeptide critical for protecting cells against oxidative stress. It is a major antioxidant in the body and an important regulator of cell proliferation, gene transcription, and apoptosis (Rana et al., 2002; Biswas & Rahman, 2009). GSH is necessary for detoxification of xenobiotics, carcinogens, and maintenance of immunity. Accumulation of oxidized form of glutathione (GSSG) leads to the activation of transcription factor nuclear factor kappa B (NF-kB) stimulating stress and inflammatory response, and cell survival (Dellhale et al., 2004). The conversion of GSSG to GSH, catalyzed by glutathione reductase, is inhibited by DTC which also inactivate several different transcription factors principally, the NF-kB and hypoxia inducible factor (Haddad, 2002 & 2003; Biswas & Rahman, 2009). PDTC is a popular inhibitor of transcription factor NF-kB which modulates the expression of many enzymes and proteins including nitric oxide synthase, heat shock protein 70 (HSP70), and induces endoplasmic reticulum stress (Schreck et al., 1992; Cvek & Dvorak, 2007; Chen et al., 2010; Cotogni et al., 2010). Prevention of binding of NF-kB to DNA induces apoptosis. DTC inhibit proteosome dependent protein degradation (Wang et al, 2006, 2011; Lovborg et al, 2006; Daniel et al, 2007; Chou et al, 2008) and promote peptide amidation (Mains et al., 1986). Thiram increases oxidative stress and induces formation of lipid peroxides, protein carbonyls, and stimulates changes in membrane potential of cells leading to ion influx inducing cell death (Erl et al., 2000; Sook Han et al., 2003; Grosicka et al., 2005). Similarly, disulfiram also induces oxidative stress that changes mitochondrial permeability leading to mitochondrial injury (Balakirev and Zimmer, 2001). A number of enzymes are inhibited by DTC which include cyclooxygenase, (Lee et al., 2002), heme oxygenase (Kushida et al, 2002), cytochrome P450, superoxide dismutase, glutathione reductase, and caspase (Dalvi et al., 2002; Cvek & Dvorak, 2007; Seefeldt et al., 2009). The superoxide dismutase inhibitory activity of thiram and disulfiram is implicated in their anti-angiogenic effects (Marikovsky et al., 2002; Shian et al., 2003). The aldehyde dehydrogenase inhibitory activity of disulfiram is the basis of its therapeutic efficacy against alcoholism (Edwards et al., 1991; Cvek & Dvorak, 2007). Disulfiram also suppresses matrix metalloproteinase (MMP) expression in osteosarcoma cells through modulation of NF-kB and activator protein-1, and possibly its metal chelating properties (Cho et al., 2007).

3.1 Neuropathic effects

Peripheral neuropathy induced by DTC is a major toxic effect which has been reported in humans and animals (Frisoni & Di Monda, 1989). Many DTC pesticides including several dialkyl dithiocarbamates and EBDTC are implicated in inducing Parkinson's-like neuropathy. The ability of DTC to inhibit acetylcholine esterase, an enzyme responsible for degradation of the neurotransmitter acetylcholine, was considered to cause neuropathy (Edwards et al., 1991), but later studies did not substantiate this mode of action. However, Viviani et al., (2008) using adrenomedullary PC12 cells showed propineb, an EBTC, to induce acetylcholine release which is mediated through depolymerization of cytoskeletal

actins. Since most DTC compounds can metabolize to CS_2, their neuropathic effects were thought to be mediated by this metabolite alone. Johnson et al. (1998) showed cross linking of neurofilament proteins induced by CS_2 as a mechanism for its axonopathic and neurotoxic effects. However, metabolic studies with different DTC have not supported the role of CS_2 as the sole mechanism for their neurotoxic effects (SAP report, 2001). Stimulation of non selective cation channels by thiram, ziram, and maneb cause the influx of Ca^{++} and Cu^{++} into mitochondria increasing oxidative stress which induce apoptosis of PC12 cells and dopaminergic neuronal damage (Sook Han et al., 2003; Barlow et al., 2005). DTC metal complexes induce dopamine oxidation and produce intraneuronal oxidative stress leading to neuronal damage (Fitsanakis et al., 2002). Since DTC chelate heavy metals such as Cu, Zn, and Fe, leading to their intraneuronal accumulations, these metals have been implicated in promoting lipid peroxidation, oxidative stress, and enzyme inhibitions causing neurotoxic effects (Nobel et al., 1995; Valentine et al., 2009; Viquez et al, 2009; Viola-Rhenals et al., 2007). Increased production of reactive oxygen species by the actions of mancozeb and zineb is also implicated in their neuronal toxicities (Domico et al., 2007). Maneb, an EBDTC containing Mn^{+2}, was found to induce nitric oxide production, lipid peroxidation, and cause Parkinson's like disease syndrome in mice (Gupta et al., 2010). Mancozeb, thiram, and disulfiram cause membrane potential changes and impair ATP dependent glutamate uptake into the synaptic vesicles and prevent binding of glutamate to its receptors resulting in excitotoxic effects in the brain (Nagendra et al., 1997; Vaccari et al., 1999). Ubiquitin proteosome pathway maintains the balance of cellular proteins through their degradation since abnormal accumulation of protein can interfere with cell functions (Myung et al, 2001). Both disulfiram and ziram inhibit ubiquitin proteosomal pathways causing dopaminergic cell damage (Lovborg et al., 2006; Chou et al., 2008). Disulfiram also reduces the activity of brain enzyme peptidoglycine-5 hydroxylating monooxygenase and alpha-melanocyte stimulating hormones affecting behavioral changes in rats (Rahman et al., 1997).

3.2 Reproductive and endocrine disruptive effects

Chemicals which interfere with endocrine functions altering the synthesis, metabolism, and secretion of hormones, or their target organ effects, are called endocrine disruptors (Diamanti-Kandarakis et al., 2009). There are several reports suggesting the endocrine disruptive actions of DTC. Studies by Stoker et al (1993; 2003) showed that thiram induces ovulatory delay and affects fecundity in rats. Some of these effects of DTC are related to the interference of enzymes involved in the synthesis of catecholamines which regulate neuroendocrine functions (Stoker et al., 1993; Goldman et al., 1994). Thiram inhibits spermatogenesis in rats (Mishra et al., 1998). Mancozeb affects ovarian function and disrupts the estrous cycle, inducing infertility in rats (Cooper et al., 1999; Cecconi et al., 2007). The hypothyroid and antithyroid effects of zineb and mancozeb are associated with their metabolite ethinylthiourea (ETU) (Houeto et al., 1995; US EPA, 2001; Panganiban et al., 2004; Axelstad et al, 2011). Both thiram and disulfiram inhibit 11β hydroxyl steroid dehydrogenase 2, an enzyme that catalyzes conversion of hormonally active glucocorticoids, cortisol and corticosterone, to their inactive metabolites, and interfere with binding to their receptors (Atansov et al., 2003; Garbrecht et al., 2006).

3.3 Immunomodulatory effects

The immunomodulatory effects of DTC can be largely related to their ability to prevent activation of transcription factors and other signaling mechanisms. Lipopolysaccharide

induced tumor necrosis factor alpha production by promyelocytic THP-1 cells is inhibited by mancozeb (Corsini et al., 2006). Ziram interferes with the lytic function of natural killer cells through modification of their cell surface proteins such as CD16 which is necessary for their binding to target cells (Taylor & Whalen, 2009) and potentiates Concanavalin A induced interferon-γ and interleukin-6 production by the vascular lymph node cells (De Jong et al., 2002). In U937 lymphoma cells, ziram produces its toxic effects by activating intracellular caspase-3 enzyme and mitochondrial cytochrome c release which lead to their apoptosis (Li et al., 2010). However, with respect to cellular immunity, studies have shown DTC induce activation of T cells, natural killer (NK) cells, and increase immunoglobulin secretion by B cells (Corsini et al., 2006, 2008). Thiram induces lymphocyte sensitization, hypersensitivity, and allergic dermatitis (Saunders & Watkins, 2001). Although the mechanism of allergic dermatitis induced by thiram is not well understood, the involvement of T cells is likely. DTC can act as haptens which on conjugating to proteins may induce allergic hypersensitivity. Cytofluorometric study by Lombardi et al. (1991) showed increased splenic population of T cytotoxic/suppressor cells induced by dimethyl and diethyl DTC. The effects of different DTC on immunity needs better understanding.

3.4 Carcinogenic and teratogenic effects

The EBDTC in general, are considered to be carcinogenic because of their metabolite ETU that produces thyroid and pituitary tumors (Houeto et al., 1995). Steenland et al. (1997) showed the genotoxic effects of mancozeb indicated by increased chromosomal translocations and sister chromatid exchange in the blood cells of workers exposed to it. In vitro studies with zineb on human lymphocytes and CHO cells showed it to induce DNA strand breaks suggesting its carcinogenic potential in the event that the affected cells survive and propagate (Soloneski et al., 2002; 2003; Gonzalez et al., 2003). Calviello et al. (2006) showed DNA single strand breaks in rat fibroblasts exposed to mancozeb. DNA breaks and chromosomal aberration induced by thiram in CHO cells was reported by Mosseso et al. (1994), but in vivo tests employing different doses of ferbam, which is similar to thiram, showed no significant induction of aneuploidy (Shanthi & Krishnamoorthy, 2002). Although the recovery of DTC damaged cells and their survival is important for carcinogenicity, there is meagre evidence in its favor (Hasegawa et al., 1988). Studies on the effects of DTC on developing rat embryos show that these agents induce cleft palate, wavy rib formation, and long bone distortions (Roll, 1971). Several recent studies have shown sodium metam, thiram, and disulfiram caused notochord distortions, and craniofacial abnormalities in zebra fish embryos (Haendel et al., 2004; Tilton, et al., 2006; Teraoka et al., 2006; van Boxtel et al., 2010). Some effects of these chemicals on craniofacial malformation are attributed to their down-regulating effects on genes related to transforming growth factor beta-1 (TGF-β1) which plays an important role in skeletal morphogenesis. Inhibition of lysyl oxidase, a Cu^{++} dependent enzyme essential for collagen cross linking, by the chelating actions of DTC is also suggested as another possible mechanism in the induction of craniofacial abnormalities (van Boxtel et al., 2010).

4. DTC effects on avian systems

The major bulk of research on DTC has been carried out using mammalian models or cells. But their effect on avian growth plate cartilage is noteworthy because in relatively small doses and short exposure time, certain DTC can induce cartilage defects in growing birds

which render them lame (Vargas et al., 1983). The teratogenic and embryo toxic effects of DTC on avian system was recognized as early as 1955 when researchers noticed exposure to thiram caused leg problems in poultry (Waibel et al., 1955). These effects of thiram also were observed in later years (Page, 1975; Guitart et al., 1996). With the identification of tibial dyschondroplasia (TD), a defect of endochondral bone formation in young poultry by Leach & Nesheim (1965), correlations showed that DTC caused poultry leg problems (Vargas et al., 1983). Subsequent studies by different investigators showed that both dimethyl and diethyl DTC caused TD in post hatch poultry (Veltmann et al., 1985; Edwards, 1987; Orth & Cook, 1994; Rath et al., 2004). With TD, the proximal growth plates of the tibia and tibio-tarsal bones fail to ossify leading to the retention of unresolved cartilage. Feeding post hatch chickens diets containing thiram 50-100 mg /kg feed for a day or two is sufficient to induce TD (Rath et al., 2004; 2005; 2007b) (Figure 2). The incidence and severity of the disease is related to the age of the chicks; during the early phase of growth when the bones are fast growing, the effects are more severe. Subsequent studies showed that the dimeric and trimeric analogs such as thiram, disulfiram, ferbam, and ziram would induce this defect, where as the monomeric DTC such as potassium dimethyl dithiocarbamate, sodium metam, or PDTC were ineffective or less potent in similar concentrations (Rath et al., 2004; 2007b). The induction of TD by thiram is dose dependent. Feeding a thiram containing diet was more effective in inducing tibial dyschondroplasia than their subcutaneous administration (unpublished observation). Thiram reduces feed intake resulting in body weight loss but it does not stop longitudinal growth of bones. Whether, feed intake is affected through the influence of thiram on hypothalamic mechanisms is not known but based on its demonstrated neuroendocrine effects (Stoker et al., 1993), it may be a possibility. Thiram causes an elevation in serum corticosterone level (Rath et al., 2004) which can be related to its inhibitory effect on 11β-hydroxysteroid dehydrogenase-2 that mediates the conversion of corticosterone to its inactive metabolite 11-hydroxycorticosterone (Atanasov et al., 2003). Endochondral bone formation is a complex process which involves an orderly transition of cartilage from proliferative to hypertrophic state when they undergo chondrolytic degeneration and replaced by osteoblast (Reddi & Anderson, 1976; Burdan et al., 2009). Angiogenesis and neovascularization of growth plate is essential for bone formation. Thiram exerts a high level of toxicity on endothelial cells inducing death of capillary vessels in the growth plate and interferes with the hypertrophic process resulting in premature death of chondrocytes. Apoptosis of growth plate chondrocytes and blood vessels are evident by histochemical staining and the assessment of DNA fragmentation (Rath et al., 2005) (Figure 3). Treatment with thiram reduces the concentrations of enzymes and proteins associated with bone development which may be related to the cell death in growth plate (Rath et al., 2005). Both in chickens and turkeys, thiram interferes with growth plate modeling and angiogenesis by interfering with matrix metalloproteinases (MMP) production (Hasky-Negev et al., 2008; Dan et al., 2009). Vascular endothelial growth factor (VEGF) is a regulator of angiogenesis that acts through its receptors. Thiram down-regulates the expression of genes for VEGF receptor and Bcl-2, an antiapoptotic protein, in the growth plate (Rath et al., 2007a). Tian et al. (2009) showed the down-regulation of matrilin, and MMP-13 genes in growth plates of chickens that were treated with thiram. Expressions of these genes are important in growth plate maturation. Consistent with literature on the action of DTC in different systems, there was also a decrease in glutathione levels in growth plate cartilage of thiram-treated chickens (Rath et al., 2005). Comparative proteomics of growth plate tissue extracts showed decreases in several proteins in thiram-fed chickens most of which were

associated with energy metabolism, signal transduction, and secretory functions (Rasaputra et al., 2010). Down-regulation of those proteins may be responsible for chondrocyte death. The differential effect of thiram on hypertrophic chondrocytes may be related to the developmental transition of cells when they become prone to the toxic effects of DTC. Hypertrophy of chondrocytes is necessary for lengthening of bone which results in a significant change in cell volume (Farnum et al., 2002). Increases in cell volume occur from increased protein synthesis and influx of inorganic solutes, and osmolytes. The latter processes are affected by the changes in membrane permeability and increased ion channel activities. Recently, Bush

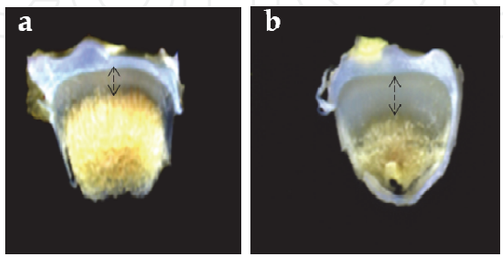

Fig. 2. Proximal tibial growth plates (arrow) of 14 day-old chickens fed either (a) a control diet or (b) a diet containing 100 mg thiram/kg feed for 48 hours between days 8 and 9 showing tibial dyschondroplasia evident by an irregular broadening of growth plate.

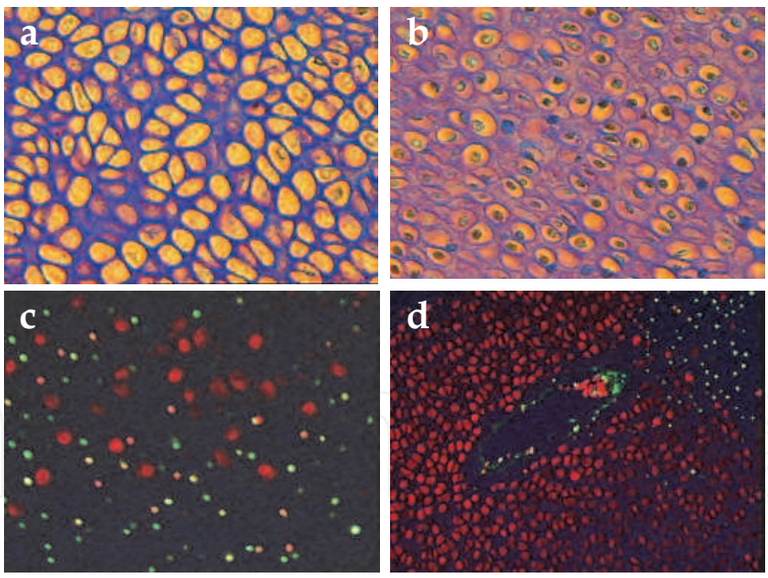

Fig. 3. Histology and histochemistry of hypertrophic zone chondrocytes of (a) normal tibial growth plate (b) thiram-induced dyschondroplastic growth plate with diminished chondrocyte volumes, pyknotic nuclei, and matrix rarefaction. (c&d) Dyschondroplastic zone chondrocytes showing terminal deoxynucleotidyl transferase mediated fluorescein dUTP nick end labeling (TUNEL) of apoptotic cells with yellow to green fluorescence and healthy chondrocytes with red fluorescence due to propidium iodide staining. (d) A dead capillary vessel surrounded by both healthy and apoptotic chondrocytes (adapted from Rath et al., 2005).

et al. (2010) showed an increased expression of Na^+ K^+ Cl^- cotransporter protein (NKCC) in hypertrophic chondrocytes. Pucci et al. (2007) also observed changes in mitochondrial membrane potentials of hypertrophic chondrocytes that permeate influx of cationic molecules. It is possible that changes in chondrocyte membrane permeability during hypertrophy facilitate higher influx of thiram into the cells inducing metabolic inhibitions, oxidative stress, and apoptosis. Thiram also can inhibit other molecular changes associated with the ossification process. Using microarray analysis of chicken growth plate, Horvat-Gordon et al. (2010) showed high expression of several genes associated with angiogenesis and oxido-reductive metabolism in hypertrophic chondrocytes. The proteins encoded by these genes such as the transferrin, matrix metalloproteinases, aldehyde dehydrogenase, lysyl oxidase, and superoxide dismutase contain metal ions that are prone to chelation by DTC which can modulate their activities and cause metabolic dysregulations. Marikovsky et al. (2002) have shown that both thiram and disulfiram interfere with angiogenesis through inhibition of superoxide dismutase.

4.1 Effects on chondrocyte culture

Proteomics is a powerful tool to identify biomarkers and understand the mechanisms of action of toxicants (Kennedy, 2002). To find whether thiram induces peptide and protein changes, the growth plate chondrocytes in culture were treated with sub lethal concentrations of thiram for 48 h. The viability of the cells were determined by monitoring the release of lactate dehydrogenase (LDH) into the culture medium as an indicator of cell damage (Rath et al., 1995) which showed no significant change at 48 h. The peptide profiles of these chondrocyte extracts were examined by means of matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS) in the *m/z* range of 1,000 to 7,000, and compared between control and thiram treated cells. Differential expression of the peptides was determined using statistical algorithms and principal component analysis by the use of ClinproTool™ software (Bruker Daltonics, Germany). Comparing approximately 50 spectral peaks, 4 showed quantitative differences in thiram treated chondrocytes with 2 peptides corresponding to *m/z* 3004.5 and 3310, elevated, and 2 corresponding to *m/z* 1778.9, 2556.3, decreased (Figures 4 & 5) (Rasaputra et al., unpublished). Although the functional significance of the changes in these peptides is currently unknown such information can be useful to identify toxicity associated peptide biomarkers. Similarly, comparing the protein profiles of control and thiram treated chondrocytes by two dimensional gel electrophoresis, several proteins were found to be decreased by thiram treatment, particularly a heat shock protein HSP70 was significantly down-regulated (Rasaputra et al., unpublished). HSP70 is necessary for protein folding and protects the cells from oxidative stress and apoptosis (Beere et al., 2000; Mosser et al., 2000; Guzhova & Margulis, 2006). Its chondroprotective effect has been shown in mammalian models (Otsuka et al., 1996; Etienne et al., 2008). It is possible that the decrement in the levels of HSP70 contributes to the loss of chondrocyte viability. In conclusion, the effect of DTC on growth plate development provides a good experimental model to study the toxicology of these compounds in skeletal system.

5. Conclusion

From the preceding discussion, it is evident that the DTC modify cellular metabolism by their direct interactions with different molecules such as signaling proteins, peptides, and

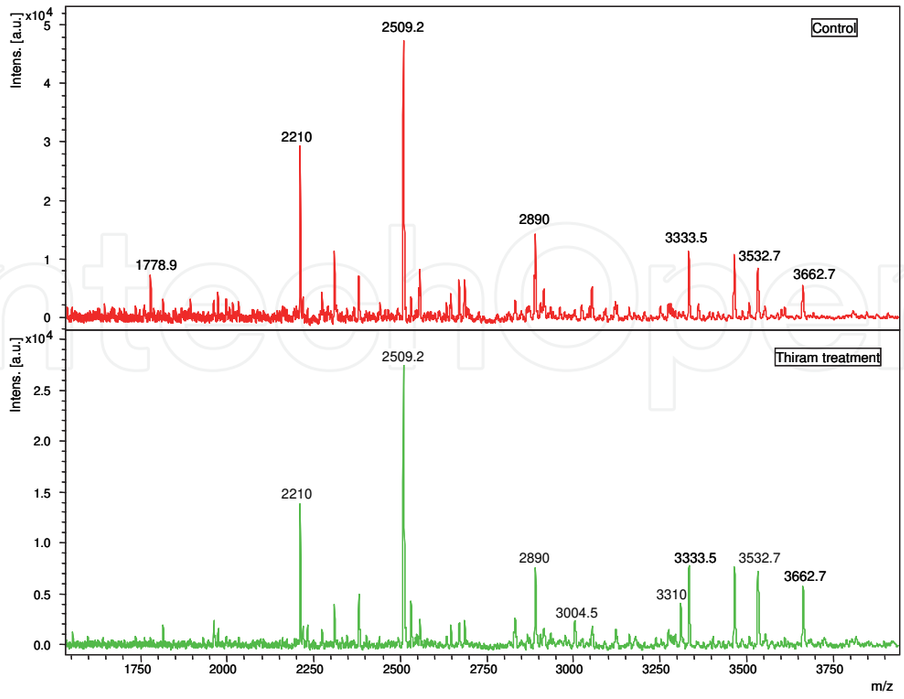

Fig. 4. The MALDI-TOF mass spectral profiles of control and thiram treated chondrocyte extracts showing peptide peaks in the *m/z* 1500-4000.

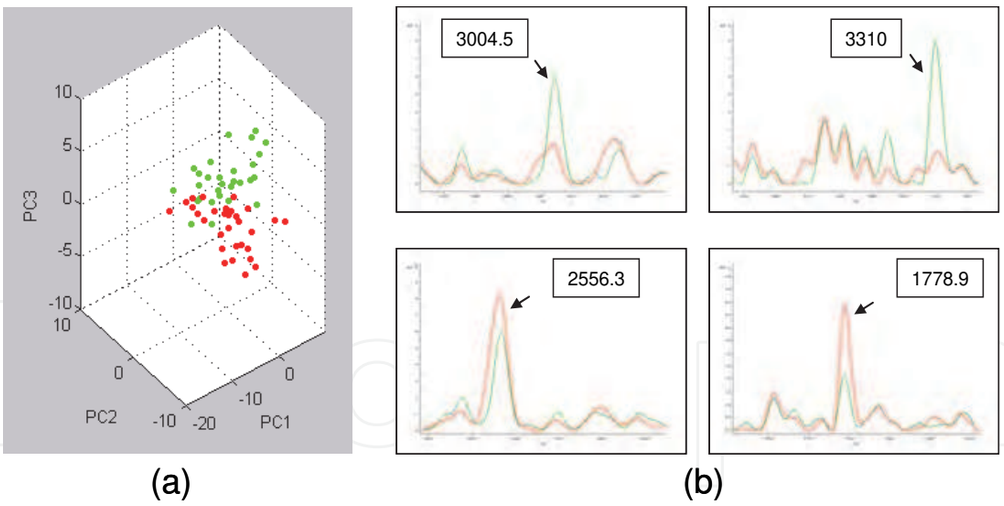

Fig. 5. (a) Principal component analysis of mass spectrum showing similarities and differences in peptide profiles of control (red) and thiram treated chondrocytes (green), and (b) profiles of the differentially expressed peptides ($P \leq 0.001$).

enzymes, and influence the oxido-reductive metabolism of the cells. Their metal chelating properties additionally, contribute to their prooxidative effects. The cells exposed to DTC experience increased oxidative stress and metabolic dysregulations leading to tissue damage, and apoptosis. The disparate vulnerability of tissues to the toxic effects of different DTC may be due to the differences in their membrane permeability and cellular constituents

interacting with these chemicals. Dividing and differentiating cells may be more susceptible to the toxic effects of DTC. Although some of their metabolites such as carbon disulfide and ethinylurea contribute to certain organ specific pathologies, it is most likely that the whole molecules are responsible for their acute toxicities. There is little evidence of the ecotoxicological hazards of these chemicals. High propensity of dithiocarbamates to modulate signal transduction mechanisms, provide the promise for their usefulness in various pharmaceutical applications.

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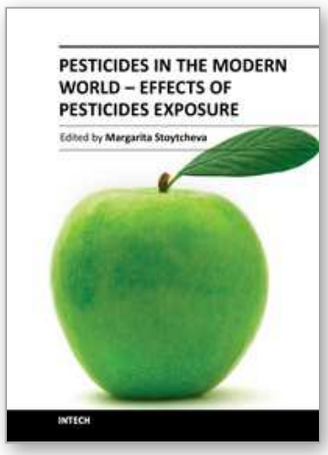

Pesticides in the Modern World - Effects of Pesticides Exposure

Edited by Dr. Margarita Stoytcheva

ISBN 978-953-307-454-2
Hard cover, 376 pages
Publisher InTech
Published online 12, September, 2011
Published in print edition September, 2011

The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950â€™s 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 livestockâ€™s yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising worldâ€™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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Narayan C. Rath, Komal S. Rasaputra, Rohana Liyanage, Gerry R. Huff and William E. Huff (2011). Dithiocarbamate Toxicity - An Appraisal, Pesticides in the Modern World - Effects of Pesticides Exposure, Dr. Margarita Stoytcheva (Ed.), ISBN: 978-953-307-454-2, InTech, Available from: http://www.intechopen.com/books/pesticides-in-the-modern-world-effects-of-pesticides-exposure/dithiocarbamate-toxicity-an-appraisal

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