Environment International 99 (2017) 29–42

Contents lists available at ScienceDirect

Environment International

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

Review article

A systematic review of Mancozeb as a reproductive and developmental hazard

Jennifer Runkle [a,d,*], Joan Flocks [b], Jeannie Economos [c], Anne L. Dunlop [d]

[a] Cooperative Institute for Climate and Satellites-North Carolina, North Carolina State University, Asheville, NC, USA
[b] Center for Governmental Responsibility, Levin College of Law, University of Florida, Gainesville, FL, USA
[c] Farmworker Association of Florida, Apopka, FL, USA
[d] Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA, USA

ARTICLE INFO

Article history:
Received 4 May 2016
Received in revised form 3 November 2016
Accepted 3 November 2016
Available online 23 November 2016

Keywords:
Mancozeb
Reproductive health
Developmental toxicant
Office of Health Assessment and Translation
systematic review framework
Pesticide registration review

ABSTRACT

Background: The potential adverse reproductive and developmental effects of Mancozeb, especially in sensitive subpopulations, have not been fully reviewed for this widely used fungicide.
Objective: To review the experimental and epidemiologic evidence for the association between exposure to Mancozeb and reproductive and developmental health outcomes using an adaptation of the National Toxicology Program's Office of Health Assessment and Translation (OHAT) systematic review framework.
Data sources: Four databases (PubMed, TOXNET, Web of Science, Google Scholar) were searched for published studies on Mancozeb. Of 403 identified articles, 30 met our inclusion criteria for systematic review.
Results: Results from in vitro studies provide evidence that Mancozeb may indirectly disrupt or impair reproduction at the cellular level and should be regarded as a reproductive toxicant. Animal studies confirm reproductive and developmental toxicity in mammals and suggest that males chronically exposed to Mancozeb experience significant changes in physiological, biochemical, and pathological processes that may lead to infertility. Epidemiological studies were limited to indirect methods of exposure assessment and examined the effect of fungicides more broadly during pre-conception, pregnancy, and birth, yielding mixed results.
Conclusions: High confidence ratings from in vitro and animal studies, in combination with moderate confidence ratings from epidemiologic studies employing indirect methods of exposure assessment, provide evidence that Mancozeb should be regarded as a suspected developmental hazard and a presumed reproductive hazard in humans. More population-based studies linking direct measures and/or biomarkers of exposure to adverse effects on male and female fertility, as well as in utero and early life development, are needed to improve the quality of the evidence base concerning the human reproductive and developmental consequences of Mancozeb exposure.

Contents

* Corresponding author at: Cooperative Institute for Climate and Satellites-North Carolina, North Carolina State University, 151 Patton Avenue, Room 500, Asheville, NC 28801-5001, USA.
E-mail address: jrrunkle@ncsu.edu (J. Runkle).

http://dx.doi.org/10.1016/j.envint.2016.11.006
0160-4120/

1. Introduction

Mancozeb, an ethylene bisdithiocarbamate (EBDC) fungicide with the degradate ethylenethiourea (ETU), was first registered in the United States in 1948 as a broad spectrum fungicide (EPA, 2005). Mancozeb has since demonstrated nearly seventy years of fungicidal efficacy in a wide range of agricultural and industrial applications, including use as a fungicide in major agricultural crops (e.g., potato, tomato, grapevine, and citrus) for roughly 400 different plant pathogens. Mancozeb is currently registered as a general use pesticide by the Environmental Protection Agency (EPA). According to a recent industry analysis, Mancozeb exhibited the fastest growing production volume accounting for >20% of the global fungicide market in 2014 (Fungicides Market, 2015). Mancozeb production is forecasted to continue to grow faster than normal by the early 2020's due to a low purchase price, increasing global demand for fruits and vegetables, and continued non-selective fungicidal efficacy (Fungicides Market, 2015). In the United States, the estimated use of Mancozeb has remained relatively stable since 2010 ranging from 4.2 and 7.2 million pounds per year for vegetable and fruit crops and orchards and grapes, respectively (U.S. Geological Survey, n.d).

Routes of exposure among the general public primarily involve limited dietary exposure through the consumption of contaminated produce (e.g., tomatoes, potatoes, citrus fruits) or drinking water. Workplace exposure to Mancozeb occurs among workers who produce the chemical and among agricultural workers following dermal contact, inhalation of dusts or fine spray, or accidental/incidental ingestion, as in eating or smoking without prior handwashing. Mancozeb is rapidly metabolized by the body and has been characterized as having low-acute toxicity in animal studies (Ellenhorn and Barceloux, 1988). However, exposure to this fungicide has been linked to a wide range of environmental health hazards including neurotoxic effects and Parkinson-like symptoms (Zhou et al., 2004) and sensitization in vulnerable populations (e.g., women and children), including thyroid hormone disruption exhibited in women chronically exposed (Goldner et al., 2010) and disregulations in fetal brain development (Nordby et al., 2005).

Mancozeb and other EBDCs have been the subject of two special EPA reviews, initiated in 1977 and 1987 because of particular health concerns, including developmental and thyroid effects caused by the common degradate ETU (EPA, 2005). In the 2005 Reregistration Eligibility decision (RED), the EPA raised several risk concerns and recognized data gaps for developmental, reproductive, and thyroid toxicity in response to exposure to Mancozeb. Since 2005, the EPA has issued final rules on tolerances for residues of Mancozeb on various crops including almonds, cabbage, lettuce, peppers, and broccoli in 2011(40 CFR Part 180 2011 ed.) and walnuts and tangerines in 2013(40 CFR Part 180 2013 ed.). In these final rules, the EPA continued to acknowledge certain data gaps for Mancozeb and ETU, especially regarding the impact of exposure on the developing thyroid and reproductive system. The 2013 final rule acknowledged results demonstrating an association between Mancozeb exposure in rat and rabbit studies and maternal mortality, spontaneous abortion, thyroid effects, maternal body weight gain decrements, and decreased pup body weight. The EPA also acknowledged fetal malformations, including hydrocephaly and domed head, observed in rat and rabbits exposed to ETU.

The longer-term toxicity of the fungicide Mancozeb and its metabolite, ETU, includes known endocrine disruptive, teratogenic, mutagenic, and carcinogenic risks (EPA, 2005; WHO, 1988). Recent toxicological evidence has shown lasting genotoxic and pre-malignant changes in human ovarian and immune cells following exposure to Mancozeb elevating concerns of potential cancer and reproductive health risks in exposed human populations (Paro et al., 2012; Srivastava et al., 2012). Experiments conducted on rodents have established that Mancozeb and ETU are capable of crossing the placental barrier with large potential to disrupt reproductive performance, cause DNA damage, and initiate tumors in fetal cells (Cecconi et al., 2007; Shukla and Arora, 2001). Belpoggi et al. (2002) demonstrated the multipotent carcinogenic potential of Mancozeb following long-term exposure in rats. Mancozeb is also a suspected endocrine disruptor associated with both hyperthyroidism and hypothyroidism (Axelstad et al., 2011; Goldner et al., 2010).

Growing evidence raises unresolved questions regarding the link between routine use of Mancozeb and human reproductive and developmental consequences. To-date no systematic review has evaluated the current state of scientific evidence linking occupational and environmental exposure to this fungicide to associated adverse reproductive health endpoints during susceptible windows of exposure, including preconception, prenatal, or early-life developmental periods. There is a general consensus among clinicians and scientists concerning the robustness of the scientific literature linking exposure to certain environmental chemicals to reproductive and developmental harms (ACOG, 2013), yet regulatory bodies have not adequately considered the potential adverse reproductive health effects in the registration and reregistration of pesticides. At the time of writing this manuscript, the US EPA has initiated the registration review for Mancozeb (case no. 0643). Registered pesticides are subject to recurrent review as required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and as amended by the Food Quality Act (FQPA) of 1996 and the Pesticide Registration Improvement (PRIA) Act of 2003 (7 U.S.C. sec. 136, et seq.). The intent behind the registration review process is to examine evidence from accumulating scientific studies and reevaluate the risks to human health and the environment of a registered pesticide.

We reviewed the literature for notable experimental and human health studies that link environmental or occupational exposure to Mancozeb to adverse reproductive and developmental health effects. Existing regulations are not often based upon consideration of the risk to human reproduction and development, particularly for chronically exposed and vulnerable populations, such as farmworkers and their children. We urge regulatory agencies to implement similar systematic review procedures that closely examine the scientific evidence on reproductive health endpoints into their risk assessment and decision-making process for registered chemicals.

2. Materials and methods

2.1. Search strategy and study selection

The systematic review utilized the PubMed database (www.ncbi.nlm.nih.gov), Google Scholar (www.google.com/scholar), TOXNET database (www.toxnet.nlm.nih.gov), and Web of Science database from 1950 through August of 2016 using the following search terms: “Mancozeb” or “dithiocarbamates” or “ethylene thiourea (ETU)” and (1) “reproductive toxicity” or “reproductive effect” or “infertility” or “sperm quality;“ (2) or “developmental toxicity” or “developmental effects”; (3) or “pregnancy” or “pregnancy effects” or “birth outcomes” or “birth defects”; (4) “in utero exposure” or “chronic exposure” or “environmental exposure” or “occupational exposure”; and (5) “endocrine disrupting” or “endocrine disruptor”. Additionally, we performed