Environment International 121 (2018) 71–84

Contents lists available at ScienceDirect

Environment International

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

Review article

The Seveso accident: A look at 40 years of health research and beyond☆

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ARTICLE INFO

Keywords:
Dioxin
TCDD
Seveso
Epidemiology
Disaster

ABSTRACT

A 1976 chemical factory explosion near Seveso, Italy exposed residents to high levels of 2,3,7,8-tetracholorodibenzo-*p*-dioxin (TCDD or dioxin). Dioxin is a known human carcinogen and potent endocrine disruptor. It is highly lipophilic and has a long half-life in humans. Much of what we know and can learn about the risks of dioxin exposure on human health arose from the tragic circumstances of Seveso. This review aims to describe the Seveso accident, summarize the results of 40 years of research on the health of the Seveso population since the accident, and discuss next-stage research on the health of Seveso residents, their children, and grandchildren.

1. Introduction

In July 1976, a chemical plant explosion near Seveso, Italy exposed locals to the highest known levels of 2,3,7,8-tetracholorodibenzo-*p*-dioxin (TCDD or dioxin) exposure to a residential population (Mocarelli, 2001; Pesatori and Bertazzi, 2012). Dioxin has been classified as a known human carcinogen by the International Agency for Research on Cancer (IARC, 1997). It is a potent endocrine disruptor, highly lipophilic, and extremely stable with a long half-life in humans of 7 to 9 years (IARC, 1997; Needham et al., 1999; Needham et al., 1997). Because it is a combustion by-product, it is a widespread environmental contaminant in industrialized areas and background exposures, while declining, are ubiquitous. Much of what we know and can learn about the risks of dioxin exposure on human health arose from the tragic circumstances of Seveso. The purpose of this paper is to describe the Seveso accident, to summarize the results of 40 years of research on the health of the Seveso population after the accident, and to discuss next-stage research on possible health effects among the residents, their children, and grandchildren.

2. The history of the Seveso accident in 1976

On Saturday, 10 July 1976 at 12:37 PM, a chemical reactor exploded at the ICMESA plant located in Meda near Seveso, Italy (25 km north of Milan) (see previous detailed descriptions (Mocarelli, 2001; Pocchiari et al., 1979)). The plant was manufacturing 2,4,5-trichlorophenol, an intermediary for cosmetics and pharmaceuticals. A runaway chemical reaction resulted in the release of an aerosol cloud that included sodium hydroxide, ethylene glycol, sodium trichlorophenate, and an estimated 15 to 30 kg of TCDD over an 18-km^2 area (di Domenico et al., 1980). Area residents in the path of the aerosol cloud developed nausea, headaches, eye irritation, and 19 children were admitted to the local hospitals with skin lesions (Signorini et al., 2000). In the ensuing weeks, the area experienced high animal and plant mortality, and nearly 200 cases of chloracne were reported among residents, mostly among children (Assennato et al., 1989).

On 25 July, a multipronged study was launched under the sponsorship of the Regione Lombardia Italy. The bioclinical investigations team from the Hospital of Desio collected blood specimens from thousands of residents for immediate clinical chemistry tests. The

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; DXA, dual-energy X-ray absorptiometry; EPIC, European Prospective Investigation into Cancer and Nutrition; IARC, International Agency for Research on Cancer; IHD, ischemic heart disease; NIH, National Institutes of Health; PBPK, physiologically-based pharmacokinetic; PHA, phytohemagglutinin (PHA); PWM, pokeweed mitogen; SWHS, Seveso Women's Health Study; SNP, single nucleotide polymorphism; SAB, spontaneous abortion; TCDD, 2,3,7,8-tetracholorodibenzo-*p*-dioxin; TSH, thyroid-stimulating hormone; TT4, total thyroxine; TEQ, toxic equivalent

☆ This paper was based on a presentation at the *25 Years of Endocrine Disruption Research: Past Lessons and Future Directions* meeting on September 18–20, 2016 as part of the National Institute of Environmental Health Sciences 50th year celebration.

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https://doi.org/10.1016/j.envint.2018.08.051
Received 30 June 2018; Received in revised form 21 August 2018; Accepted 23 August 2018
0160-4120/

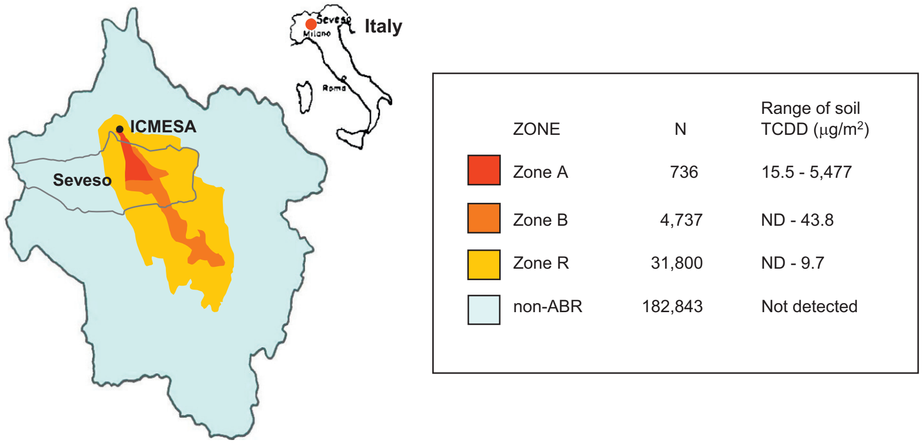

Fig. 1. Map of Seveso, Italy indicating the location of Zones A, B, R, and Non-ABR, adapted from (Mocarelli et al., 1991a).

researchers stored remaining serum for future analyses. Individuals who provided blood samples were followed up regularly until 1982 and periodically thereafter. Health effects assessed included neurological problems, infection, dermatologic lesions, and pregnancy and child health (Mocarelli et al., 1986).

In the initial absence of individual biomarker-based exposure levels, health studies from Seveso relied upon zones of residence to classify levels of exposure. The zones of residence matrix were constructed based on systematic sampling and measurement of surface soil TCDD levels. The region with the highest surface soil TCDD levels (range: 15.5–5477 μg/m^2) was classified as zone A (Mocarelli et al., 1991b). The nearby area was divided into zone B, zone R, and zone non-ABR (soil TCDD not detected; considered to be unexposed) (see Fig. 1) (Mocarelli et al., 1991a). Zone A housed 736 residents (212 families), all of whom were evacuated beginning two weeks (from July 26th to August 2nd) after the explosion; these residents underwent immediate medical examination and clinical laboratory tests. Those that lived in the most heavily exposed areas within zone A were not allowed to return to their homes, which were considered contaminated and later destroyed as part of the clean-up (Ghezzi et al., 1982). Zone B, the area of next greatest contamination, housed almost 5000 residents who were not evacuated but were warned against consuming locally-grown produce and poultry; these residents also received a medical examination and clinical laboratory tests. In addition, pregnant women and children < 12 years from zone B were relocated out of the area on a daily basis. Zone R, the least contaminated area, housed about 32,000 residents who were warned not to consume local foods (Mocarelli et al., 1992).

Although soil dioxin levels have been used as a proxy of exposure, these levels do not reflect variation in individual-level frequency and duration of contact with dioxin-contaminated media. Seveso residents are the only dioxin-exposed population for whom blood samples were collected near the time of exposure, enabling a more accurate exposure assessment of absorbed dose. In 1987, eleven years after the Seveso accident, the Centers for Disease Control and Prevention (CDC) developed an analytical method (using high-resolution gas chromatography/high-resolution mass spectrometry) to measure TCDD concentration in human serum (Patterson et al., 1987). This new method and the nearly 30,000 stored samples at the University Laboratory of the Hospital of Desio opened the door for more precise measurements of individual exposure to be examined in relation to the health of the population.

3. Seveso Women's Health Study (SWHS)

In 1996, 20 years after the explosion, a historical cohort study was initiated of the female residents (newborn to 40 years old in 1976) of zones A or B who had blood collected near the time of the explosion. The Seveso Women's Health Study (SWHS), funded by the United States National Institutes of Health (NIH) and Regione Lombardia Italy, is the only comprehensive study to date of the health of a female population exposed to TCDD. It is unique in being a large cohort with a wide range of TCDD exposure documented by individual-level serum TCDD measurements. The methods for the SWHS have been summarized previously (Eskenazi et al., 2000).

A total of 981 women participated in the first follow-up of the population (1996). The majority of women were from zone B (83%). At the time of the explosion, women in SWHS averaged 20.1 (± 11.3) years of age, 71% were postmenarcheal, 38% were parous, and < 1% were postmenopausal (see Table 1). The women were followed up again in 2008 (Warner et al., 2011) and 2014; participants did not differ from the full SWHS cohort with respect to characteristics at explosion (see Table 1). In 2014, the Seveso Second Generation Study was launched, with the goal of characterizing health impacts of in utero dioxin exposure in the children of SWHS participants. A total of 943 liveborn children (453 females, 490 males) who were born to 574 SWHS mothers after the explosion were enumerated and ranged in age from newborn to 39 years, A total of 611 children (66.4% of 920 alive and eligible) born to 402 mothers completed the study visit. The 611 child participants averaged 23.7 (range: 2–39) years of age and 51% were female.

Details of data collected for the SWHS and the Second Generation cohorts at each follow-up study are summarized in Fig. 2. For example, for the SWHS women the most recent data collection at the 2014 visit included a fasting blood draw for clinical chemistries and future studies, anthropometric and blood pressure measurements, a personal interview that included questions about her reproductive and medical history, and collection of medical records. For women with children < 18 years, the interview also included questions about the health of their children as well as demographic and lifestyle factors and medical history. For children 2 to 6 years, participation included a fasting blood draw for clinical chemistries and future studies, and anthropometric measurements. Participation for children 7 to 17 years old included a fasting blood draw, anthropometric and blood pressure measurements, a battery of computerized neuropsychological tests (Rey's Auditory Verbal Learning, Raven's Progressive Matrices, Connor's Continuous Performance, Wisconsin Card Sort) (Muriel Lezak et al., 2012), and an online self-administered questionnaire including smoking, alcohol, and caffeine habits (10 to 17 years only). Participation for children 18 years or older included fasting blood draw, anthropometric and blood pressure measurements, a personal interview that included the EPIC food frequency questionnaire (Pisani et al., 1997), and collection of medical records.