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Review Article

Reproductive Toxic Chemicals at Work and Efforts to Protect Workers' Health: A Literature Review

Kyung-Taek Rim*

Chemicals Research Bureau, Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency, Daejeon, 34122, Republic of Korea

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ABSTRACT

A huge number of chemicals are produced and used in the world, and some of them can have negative effects on the reproductive health of workers. To date, most chemicals and work environments have not been studied for their potential to have damaging effects on the workers' reproductive system. Because of the lack of information, many workers may not be aware that such problems can be related to occupational exposures. Newly industrialized countries such as Republic of Korea have rapidly amassed chemicals and other toxicants that pose health hazards, especially to the reproductive systems of workers. This literature review provides an overview of peer-reviewed literature regarding the teratogenic impact and need for safe handling of chemicals. Literature searches were performed using PubMed, Google Scholar, and ScienceDirect. Search strategies were narrowed based on author expertise and 100 articles were chosen for detailed analysis. A total of 47 articles met prespecified inclusion criteria. The majority of papers contained studies that were descriptive in nature with respect to the Medical Subject Headings (MeSH) terms and keywords: "reproductive and heath or hazard and/or workplace or workers or occupations." In the absence of complete information about the safe occupational handling of chemicals in Republic of Korea (other than a material safety data sheet), this review serves as a valuable reference for identifying and remedying potential gaps in relevant regulations. The review also proposes other public health actions including hazard surveillance and primary prevention activities such as reduction, substitution, ventilation, as well as protective equipment.

1. Introduction

Chemicals are ubiquitous substances with both positive and negative effects found in workplaces across the globe. Together with other agents (e.g., radiation and bacteria), chemicals may also negatively affect the reproductive systems of male and female workers (Table 1). Several environmental chemicals are suspected to be responsible for adverse health effects on the reproductive system in various organisms [1]. Exposure to toxicants before and after conception can affect parents, fetuses, and newborns. Pregnant women tend to be concerned about three of the most common occupational health hazards (i.e., tobacco smoke, video-display terminals, and the quality of indoor air). In addition, biological stressors such as shift work may also negatively impact workers' reproductive systems. Despite the controversies and uncertainties about these factors and the lack of data regarding other potential occupational health hazards, the consequences of toxic exposure are necessary issues that have to be delicately broached by occupational health and safety counselors in their discussions with pregnant workers [2]. It is worth noting that, with the exception of reproductive toxicants listed in the Korean Occupational Safety and Health Act (Table 2), the potentially damaging effects of chemicals to workers' reproductive systems have not been extensively reviewed in the literature.

Despite the lack of information about possible reproductive health effects, many potentially toxic substances are still used in a variety of workplaces, and many workers are exposed to such hazards every day at work. Given certain toxicant-workplace scenarios, some workers may develop sexual or reproductive problems. Because a material safety data sheet is composed of many

* Corresponding author. Chemicals Research Bureau, Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency, 339-30 Expo-ro, Yuseong-gu, Daejeon 34122, Republic of Korea.
E-mail address: rim3249@gmail.com (K.-T. Rim).

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Table 1
Examples of reproductive hazards to humans*

Hazard	Outcome
Proven reproductive hazards (based on human studies)	
Anesthetic gases	Miscarriage, death of newborn
Diethylstilbestrol	Cancer
Hepatitis B	Newborn hepatitis, liver cancer
Organic mercury	Cerebral palsy, brain malformation
Lead	Miscarriage, premature birth
Polychlorinated biphenyls	Low birth weight
Radiation	Miscarriage, brain defects, skeletal defects
Suspected reproductive hazards (based on human studies)	
Carbon monoxide	Slowed growth
Cytotoxic drugs	Miscarriage
Ethylene oxide	Miscarriage
Hexachlorophene	Birth defects
Organic solvents	Cleft palate, miscarriage, newborn infection, childhood cancer
Physical stress (including heat)	Prematurity
2,4,5-Trichlorophenol	Miscarriage
Vinyl chloride	Brain defects
Suspected reproductive hazards (based on animal studies)	
Acrylonitrile Arsenic Cadmium Dioxin Glycol ethers Inorganic mercury Organochlorine pesticides Polybrominated biphenyls	

* *Note*. Sourced and modified from "Clinical occupational medicine," by L. Rosenstock, M.R. Cullen, 1986. W. B. Saunders Company, London. Adapted with permission.

different sections, the toxicological and health information may only have one or two lines about the reproductive toxic impact of any chemical on diverse workers found in any workplace. However, the need for regulations regarding personal protective equipment for workers handling chemicals is recognized, albeit not implemented uniformly for couples who are pregnant or planning to have a child. Thus, collecting more information about the reproductive toxic impacts of chemicals in terms of occupational health and safety continues to be a thriving area of research, although data tend to be confined to individual laboratory studies published in specialty journals. In addition, there is a paucity of review articles on this topic. This review summarizes important current and pending developments in the field of known/potential reproductive toxic chemicals used in the workplace and addresses some of the potential health implications.

2. Methods

We collected information from peer-reviewed literature on the occupational health hazards posed by toxicants that may impact the reproductive systems of workers, with a view to the prevention of work-related diseases. Topics discussed included when and how reproductive damage occurred, what kinds of reproductive health problems could occur, how workers could tell if a chemical or work situation posed hazards to their reproductive health, how workers were protected, and the role of the health and safety representative. Literature searches were performed using the following sites: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (http://scholar.google.com), and ScienceDirect (http://www.sciencedirect.com). The search strategy used a combination of the following Medical Subject Headings (MeSH; National Center for Biotechnology Information, Bethesda, MD, USA) terms and keywords: "reproductive and health or hazard and/or workplace or workers or occupations and/or prevention or protection." The search results were further narrowed by reviewing titles and abstracts. Additional missing case reports were identified by reviewing the references of the review articles and bibliographies found on scholar.google.com. Disagreements in information from the articles and conference abstracts were resolved by further discussion. Based on the literature data, about 100 potential articles were found. A total of 47 articles that met the inclusion criteria were chosen for detailed analysis.

3. Results

Reproductive toxicology is focused on the risks, mechanisms, outcomes, and prevention of harmful exposure to reproductive toxic chemicals in the workplace. Preconception and postconception exposures of fertile men and women to reproductive toxic chemicals at work may detrimentally affect the parents and their children. Adverse effects on the structural and functional components of male and female reproductive systems may lead to impaired fertility or infertility of exposed workers. According to the World Health Organization (2013) [3], infertility is defined as "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. An inability to become pregnant with a live birth, within five years of exposure based upon a consistent union status, lack of contraceptive use, non-lactating and maintaining a desire for a child. Infertility may be caused by an infection in the man or woman, but often there is no obvious underlying cause." Reduced fertility may be expressed as a reduction in the number of live births, reduced odds of conception, or increased time to pregnancy [4]. Reproductive hazards in the workplace have been investigated over several decades using workplace experience and epidemiology studies, as well as studies in laboratory animals. Each of the reproductive and developmental stages can potentially be disrupted by exposure of humans or laboratory animals to specific toxicants. Various endocrine-disrupting chemicals may adversely affect the sex and reproductive organs of men and women. Furthermore, the reproductive well-being of women exposed to toxicants may be affected to the extent that negative health consequences are visible during each trimester of any potential pregnancy [5].

Data interpretation of exposure to hazardous chemicals in the workplace may be confounded by some factors, including age and ethnicity, and lifestyle factors such as smoking, diet, alcohol and recreational drug use, stress, noise, and work shifts [6]. The nature and magnitude of reproductive toxicities are often dependent on exposure levels, but these factors are difficult to assess in an occupational setting. Age is another confounder in assessing the health hazard posed by chemicals to the reproductive systems of females. Using ionizing radiation as an example, older women may have a higher cumulative exposure than younger women. The same analogy may hold true for chemicals [7]. Paternal exposure could also contribute to developmental toxicity, but it may be difficult to assess the impact of separate maternal and paternal exposures. If only limited information exists on the potential human reproductive effects of chemicals, it may then be necessary to rely on data from laboratory animals. Many examples exist in the scientific literature of chemicals that induce reproductive and developmental toxicities, and the predictive value of these animals has proven to be useful in the safety assessment of chemicals [8]. It is important to have an understanding of these differences and recognize potential limitations in species extrapolation such as sperm count and concentration, motility, and chromosome morphology [8,9]. Developmental studies of toxicity in laboratory animals showed the importance of the following considerations: (1) divergent differentiation of structure, function, and physiology across species; (2)

Table 2
Reproductive toxic chemicals listed in the Occupational Safety and Health Act in Republic of Korea*

Category	Chemical name	CAS No.
1A†	Lead and inorganic compounds, as Pb	7439-92-1
	2-Bromopropane	75-26-3
	Lead arsenate, as $Pb(AsO_4)_2$	7784-40-9
	Warfarin	81-81-2
	Carbon monoxide	630-08-0
	Lead chromate, as Cr	7758-97-6
	Lead chromate, as Pb	
1B‡	Nickel carbonyl, as Ni	13463-39-3
	Nitrobenzene	98-95-3
	N,*N*-Dimethyl acetamide	127-19-5
	Dimethylformamide	68-12-2
	Di-*n*-butyl phthalate	84-74-2
	Di(2-ethylhexyl)phthalate	117-81-7
	2-Methoxyethanol	109-86-4
	Benomyl	17804-35-2
	Benzo(a) pyrene	50-32-8
	Borates tetrasodium salts (anhydrous)	1330-43-4
	Borates tetrasodium salts (pentahydrate)	12179-04-3
	Borates tetrasodium salts (decahydrate)	1303-96-4
	1-Bromopropane	106-94-5
	Boron oxide	1303-86-2
	Elemental and inorganic forms of mercury (all forms except aryl and alkyl compounds)	7439-97-6
	2-Ethoxyethanol	110-80-5
	2-Ethoxyethyl acetate	111-15-9
	Ethylene glycol methyl ether acetate	110-49-6
	2,3-Epoxy-1-propanol	556-52-5
	Vanadium pentoxide (respirable fraction or fume; inhalable fraction)	1314-62-1
	1,2,3-Trichloropropane	96-18-4
	Formamide	75-12-7
2§	*n*-Hexane	110-54-3
	Nitrotoluene (*o*-, *m*-, *p*-isomers)	88-72-2
	Dinitrotoluene	25321-14-6
	Methyl isocyanate	624-83-9
	Cyclohexylamine	108-91-8
	3-Amino-1,2,4-triazole (or Amitrole)	61-82-5
	Acrylamide (inhalable fraction and vapor)	79-06-1
	Allyl glycidyl ether	106-92-3
	Carbon disulfide	75-15-0
	Cadmium and compounds, as Cd (respirable fraction)	7440-43-9
	Chloroform	67-66-3
	Toluene	108-88-3
	Phenylethylene	100-42-5
	Piperazine dihydrochloride	142-64-3
	2-Hexanone	591-78-6
Effects on or via lactation‖	Lindane	58-89-9

* *Note*. From "Exposure criteria for chemicals and physical factors. MoEL Public Notice No. 2016-41," by Ministry of Employment and Labor (MoEL), Sejong, Republic of Korea, 2016. MoEL. Reprinted with permission.

† It is KNOWN to have produced an adverse effect on reproductive ability or capacity or on development in humans. The placing of the substance in this category is largely based on evidence from human studies.

‡ It is PRESUMED to produce an adverse effect on reproductive ability or capacity or on development in humans. The placing of the substance in this category is largely based on evidence from experimental animals.

§ This category includes substances for which there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on reproductive ability or capacity or on development, and when the evidence is not sufficiently convincing to place the substance in Category 1.

‖ Effects on or via lactation are allocated to a separate single category. This classification can be assigned on the basis of (1) absorption, metabolism, distribution, and excretion studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk; and/or (2) results of one- or two-generation studies in animals that provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or (3) human evidence indicating a hazard to babies during the lactation period.

lack of understanding of species differences in functional ontogeny; and (3) lack of common end points and milestones across species [10]. Despite these potential limitations, human occupational and environmental experience, epidemiology studies, and often laboratory animal studies with reproductive toxic chemicals have identified lots of reproductive issues, resulting in the development of health and safety regulations and guidelines designed to protect workers from reproductive hazards.

The data available suggest a drop in the success rate of *in vitro* fertilization for parents exposed to some of the reproductive toxic chemicals as compared to parents who were not exposed to such chemicals. Existing positive findings encourage in advising that subfertile individuals, who are planning to go for the *in vitro* fertilization, should reduce toxic exposure well in advance by adopting positive lifestyle and work environment [11].

3.1. Female reproductive toxicants

Exposure to industrial chemicals can compromise reproductive functions in women. Chemicals that target the ovary can, therefore, have a significant effect on fertility, menstrual (estrous) cyclicity, and the timing of puberty and menopause. The ovary is a complex structure composed of multiple cell types (e.g., granulosa, theca, and interstitial cells) and follicles in varying developmental stages (e.g., primordial, primary, secondary, antral, and corpora lutea). Industries with a reported increased risk of the adverse reproductive outcome in exposed women without linkage to specific exposures are listed in Table 3. The impact of occupational exposure on the female reproductive system is less well-known than that for the male reproductive system, because germ-cell production in a woman is difficult to monitor, and possible indicators (i.e., amenorrhea or irregular menstruation) frequently occur enough; thus, for such a variety of reasons linking these and occupational exposure is difficult [12]. It is also difficult to ascertain if the cause is due to maternal or embryonic deficiencies or abnormalities, or to an external environmental effect. The mother may transfer chemical agents, including active metabolites, to the fetus by a variety of mechanisms, adversely affecting development. Transport of male and female germ cells to the site of fertilization in the oviduct (fallopian tube), and the transport of the fertilized egg to the site of implantation and development in the uterus are also functions that can be disrupted by reproductive toxicants. Hormonal control of the duration of pregnancy may be shortened or lengthened by toxicants, resulting in potential adverse effects on the fetus. Therefore, a variety of targets exist for industrial chemicals to disrupt female reproduction and development of the fetus, pointing to the need for additional research to help mitigate potential risks to women in the workplace. Table 4 presents examples of substances observed to induce adverse reproductive outcomes following exposure during pregnancy. Neonates and young

Table 3
Industries with a reported increased risk of adverse reproductive outcome in exposed women, without linkage to specific exposures*

Industry	Reported outcome
Rubber industry Leather industry Chemical industry Electronics industry (in solderers) Metal works	Spontaneous abortion
Laboratory work	Spontaneous abortion; birth defects
Construction Transportation Communications Agriculture and horticulture	Birth defects
Jobs with mixed solvent exposures	Birth defects; spontaneous abortion
Textiles	Spontaneous abortion

* *Note*. Sourced and modified from "Preventing occupational disease and injury," by J.L. Weeks, B.S. Levy, G.R. Wagner, 1991. American Public Health Association; Washington, DC. Adapted with permission.

children who are still in the process of developing may be exposed directly to industrial chemicals in the case of contamination of air, water, foodstuffs, soil, or even contaminated clothing worn by parents. Adverse effects on development may also be induced through inheritance of genetic damage of the germ cells of one or both parents. The primary manifestations of developmental toxicity are embryo/fetal death, malformations (birth defects), growth retardation, and developmental delay. Adverse fetal outcomes may also include preterm delivery, altered sex ratio, and childhood cancer. The induction of adverse structural changes during development is known as teratology; chemicals that induce such effects are known as teratogens. The linkage of limb abnormalities with thalidomide exposure was among the first examples of environmental factors identified as causing congenital defects [13]. Exposure to toxic chemicals during pregnancy and breastfeeding is ubiquitous and is a threat to healthy human reproduction. Discrimination, other social factors, economic factors, and occupation impact risk of exposure and harm. The global health and economic burden related to toxic industrial chemicals is more than millions of deaths and billions of dollars every year [14]. A previous study investigated the occupational health of female workers in pharmaceutical industries with the aim of proposing protective measures for the occupational health. The study concluded that strengthening the supervision of labor protection for female workers, including technical measures of occupational hazards control and health-related knowledge, and improving the occupational health of female workers are necessary [15].

Table 4
Examples of substances observed to induce adverse reproductive outcomes following exposure during pregnancy*

Chemicals	Occupations where exposure may occur
Alkylating agents	Drug workers
Anesthetic gases†	Operating room personnel (including dental and veterinary workers)
Arsenic	Agricultural workers
Benzene	Chemical workers, laboratory technicians
Carbon monoxide	Outside workers, offices with smokers
Chlorinated hydrocarbons	Laboratory workers, craft workers
Diethylstilbestrol†	Drug workers
Dimethyl sulfoxide	Laboratory workers
Dioxin†	Agricultural workers
Infectious agents	Health-care workers, social workers, teachers, animal handlers, meat cutters
Rubella virus†	Inspectors, laundry workers
Cytomegalovirus	Health-care workers
Herpesvirus hominis	Health-care workers, laboratory workers, drug workers
Toxoplasma	Health-care workers, laboratory workers
Syphilis†	Health (antenatal) care workers
Ionizing radiation†	X-ray technicians and technologists, atomic workers, drug workers
Organic mercury compounds	Workers in coal-fired power stations, waste incinerators
Organophosphate	Agricultural workers
Pesticides	Agricultural workers
Parathion	Agricultural workers
Captan	Fungicide manufacturing workers
Carbaryl	Fungicide manufacturing workers, agricultural workers
Polychlorinated biphenyls†	Electrical workers, microscopists (immersion oil)

* *Note*. Sourced and modified from "Environmental and occupational medicine," by W.N. Rom, 1983. Little, Brown and Company, Boston, MA. Adapted with permission.
† Human effects noted.

Preconception care involves health promotion to reduce risk factors that might affect women and couples of childbearing ages. The risk factors for adverse reproductive outcomes include recognized genetic diseases in the family or the individual, previous congenital diseases, miscarriage, prematurity, fetal growth restriction, infertility, chronic maternal diseases, lifestyle, and occupational or environmental factors. At present, there is increasing interest in offering a global intervention in this field. Recently, a qualitative study was conducted among women of childbearing age and health-care professionals. The results indicate the presence of many barriers and a lack of awareness of preconception health relating to women, health-care professionals, and policies. In addition, it was indicated that several barriers influence preconception care. Moreover, a lack of awareness of preconception health and care among women of childbearing age and health-care professionals emerges [16].

3.2. Male reproductive toxicants

The human testis is a known target organ for toxicant-induced testicular injury resulting from exposure to industrial chemicals. This susceptibility is due to the high rates of proliferation, differentiation, as well as a metabolic activity associated with the production of large quantities of mature sperm. Within the testis, the Leydig, Sertoli, and germ cells are three main target cells for toxicants to disrupt spermatogenesis. Numerous chemicals target various cell types, resulting in germ-cell apoptosis and spermatogenic failure. Examples of chemicals toxic to the male reproductive system are presented in Table 5.

3.3. Metals

Copper is known to be a reproductive toxicant because it affects the motility of human sperm *in vitro*. Sperm motility showed a significant decrease in the concentration over 1 mmol compared with the control [17]. Developmental toxicity of certain compounds may partly be due to maternal toxicity resulting in alterations in zinc (Zn) metabolism that affects the developing fetus. Developmentally toxic doses of 2-ethylhexanoic acid, 2-ethylhexanol, and valproic acid on Zn metabolism were investigated in pregnant rats, and the results supported the hypothesis that certain chemicals that induce maternal toxicity act, in part, to influence embryonic Zn metabolism and trigger abnormal development. Importantly, the teratogenic effects of these chemicals can be modulated by dietary Zn intake [18].

3.4. Nanomaterials

There have been published reports on the reproductive and developmental toxicities of silver nanoparticles (AgNPs) in laboratory animals. Maternal injection of AgNPs delayed physical development and impaired cognitive behavior in offspring. Ag accumulated in the testes after administration of AgNPs. AgNPs were identified in the visceral yolk sac after administration during early gestation in mice. Radiolabeled AgNPs were detected in placenta, breast milk, and prenatal and postnatal offspring after injection during late gestation in rats. Because Ag in the ionic form, and possibly also particles, was suggested to be bioavailable, further studies using new methodologies and the relevant routes and doses for human exposure are required [19]. It was clarified whether maternal inhalation of engineered NPs might constitute a hazard to pregnancy and fetal development. It is plausible that NP may translocate from the respiratory tract to the placenta and fetus, but also that adverse effects may occur secondarily to maternal inflammatory responses. The limited study describes several organ

Table 5
Examples of agents toxic to the male reproductive system*

Chemical hazards	Species effect observed (h = humans, a = animals)	Examples of occupations where hazards may occur
Alcohol	h	Social hazard
Alkylating agents	h, a	Chemical and drug manufacturing
Anesthetic gases nitrous oxide	a, h	Medical, dental, and veterinary workers
Cadmium	h, a	Storage batteries, smelter workers
Carbon disulfide	h, a	Viscose rayon manufacture, soil treaters
Carbon tetrachloride	a	Chemical laboratories, dry cleaners
Diethylstilbestrol (DES)	a, h	DES manufacturers
Chloroprene	h, a	Rubber workers
Ethylene oxide	a, h	Health-care workers (disinfectants), users of epoxy resins
Hair dyes	a	Cosmetic manufacturers, hairdressers, and barbers
Lead	h, a	Storage batteries, policeman, smelter workers
Manganese	h	Welders, ore smelters, and roasters
Nickel	a	Smelters, welders
Organic mercury compounds	a	Pesticide workers
Tris (flame retardants)	a, h	Clothing and textile work
Pesticides	a, h	Farmworkers, pesticide manufacturers
Dibromochloropropane	–	Exterminators
Vinyl chloride	h	Polyvinylchloride manufacture and processing
Elevated carbon dioxide	a	Brewery workers, chemical manufacture
Elevated temperature	h, a	Bakers, glassblowers, foundry, and oven workers
Microwaves	h, a	Radar operators, flight crew or pilots, transmitter operators
X-irradiation	h, a	Health workers, radiation workers

* Sourced and modified by Rom WN. Environmental and occupational medicine. Boston, MA: Little, Brown and Company; 1983.

systems in the offspring to be potentially sensitive to maternal inhalation of particles, but large uncertainties exist about the implications for embryo–fetal development. Considering the increased production and application of NPs and related consumer products, a testing strategy for NP should be established [20]. The associations between titanium and silver concentrations in maternal hair and risks of neural tube defects were examined in the offspring. Maternal exposure to titanium during the periconceptional period was associated with an increased neural tube defect risk in offspring, which may be partly mediated through maternal dietary habits [21].

3.5. Organic solvents

Solvents are used as degreasers; are constituents of paints, varnishes, lacquers, inks, aerosol spray products, dyes, adhesives, fuels, and fuel additives; and are intermediates in chemical syntheses [22]. Their small molecular size and lack of charge make inhalation a major route of exposure, and they are readily absorbed through the lungs, gastrointestinal tract, and skin. Virtually all solvents can cause adverse effects to reproductive health. The azo textile dye Disperse Red 1 caused adverse effects in the regeneration and reproduction of newborn and adult specimens [23]. Benzene, a known human carcinogen for leukemia, and arsine (AsH_3), a hematologic toxin, were not detected at silicon wafer fabrication sites. *N*-butyl acetate was also not detected, but fluorides and propylene glycol monomethyl ether acetate existed in small amounts in the workplace. Because unconditional exposures during spills and maintenance tasks and by-product chemicals were not included, further studies might be required [24]. Human exposure to di-*n*-butyl phthalate (DBP) estimates range from 0.007 mg/kg/d to 0.01 mg/kg/d in the general population and up to 0.233 mg/kg/d in patients taking DBP-coated medications. Because levels of phthalates tend to be higher in women, evaluating ovarian effects of DBP exposure is of great importance, and it was shown that DBP could disrupt ovarian function in mice at doses relevant to humans [25]. Animal experiments and some human studies indicate that polybrominated diphenyl ethers (PBDEs) may adversely affect male reproductive function. To assess the association between PBDE exposure and reproductive hormones in a male adult cohort, it was suggested that PBDE exposure might affect reproductive hormones in older men [26].

3.6. Pesticides

Nearly 50% of the world's labor force is employed in agriculture. Over the past 50 years, agriculture has deeply changed with a massive utilization of pesticides and fertilizers to enhance crop protection and production, food quality, and food preservation. Pesticides are unique chemicals as they are intrinsically toxic for several biological targets, are deliberately spread into the environment, and their toxicity has a limited species selectivity. Pesticide toxicities are responsible for acute poisonings as well as for long-term health effects, including cancer and adverse effects on reproduction. Occupational exposure to pesticides in agriculture concerns product distributors, mixers and loaders, applicators, bystanders, and rural workers re-entering the fields shortly after treatment. Assessing and managing the occupational health risks posed by the use of pesticides in agriculture is a complex but essential task for occupational toxicologists. The experience of many countries has shown that prevention of health risk caused by pesticides is technically feasible and economically rewarding for workers. Risk management of pesticide is a prerequisite for safe use of these compounds [27]. Several recent epidemiology studies have evaluated exposure to a variety of pesticides, and they have identified associations between pesticide exposure and decreased sperm concentration, motility, and morphology. Concomitant exposure to several different pesticides may also present an issue. Swan et al [28] measured metabolites of eight current-use, persistent pesticides to serve as potential biomarkers of pesticide exposure and found an association with semen quality in farmers from an area with high pesticide use. By contrast, a review conducted by Perry [29] that evaluated low-level occupational exposure to a variety of pesticides concluded that epidemiologic

evidence is far equivocal due to the small number of published studies. In another study, Bapayeva et al [30] assessed the puberty of females living in cotton-growing regions where organochlorine pesticides are widely used. The study showed the adverse effect of organochlorine pesticides on the development of the female reproductive system during puberty. While the acute toxicity of pesticides has been well documented, relatively little is known about the effects of chronic pesticide exposure on health. Given the indisputable chronic exposure of vulnerable groups to organophosphate compounds, including pregnant women, the fetus, and young children, the potential adverse effects are considerable [31]. The association of occupational exposure to current-use pesticides with reproductive hormones, semen quality, and genital measures was investigated among young men. It supposed that chronic occupational exposure to modern pesticides might affect reproductive outcomes in this group [32].

3.7. Endocrine disruptors

Research into how exposure to "endocrine disruptor chemicals" affects human health is attracting increasing attention among scientists as these contaminants are so widespread in work environment and can have far-reaching effects on mental and physical health. There are specific occupational exposures to bisphenol A (BPA), styrene, pesticides, metals, dioxins, phthalates, and others. Although the exposure occurs in different ways, the toxic mechanisms of action vary widely, and it is hard to establish precisely the conditions of occupational exposure; significant correlations are nevertheless evident among the potential dose and its effects, and further studies are certainly needed in this area [33]. Fiandanese et al [34] investigated the effects of maternal exposure to the plasticizer di(2-ethylhexyl) phthalate and the organic industrial compounds polychlorinated biphenyls, alone and in combination, on the reproductive function of male mouse offspring. Their study illustrated the complex action of a di(2-ethylhexyl) phthalate/polychlorinated biphenyl mixture and its effects on the male reproductive system, indicating the need for research on the reproductive hazards of combined endocrine disruptors. BPA has been associated with a decrease in sperm quality. The association between BPA and 35 measures of semen quality was estimated among reproductive-aged men between 2005 and 2009. A negative relationship between BPA and DNA fragmentation was the sole significant finding in the adjusted linear regression ($\beta = -0.0544$, $p = 0.035$) and suggested less sperm DNA damage [35].

3.8. Genotoxic/nongenotoxic carcinogens to reproductive and developmental stages

Carcinogens/mutagens may pose a health hazard to the mother and fetus during pregnancy and may also have long-term effects on newborns. A substance that prevents the normal development of a fetus is called a teratogen. Synthetic chemicals have garnered increased attention in recent years because of reports of a rise in testicular cancer, abnormalities of the male reproductive tract, and decreases in semen quality. A large number of natural and synthetic chemicals have now been studied and reported to disrupt the normal functioning of the reproductive system, resulting in adverse effects on the hormone-responsive target tissue and organs in both humans and animals [36]. Information on human transplacental exposure to carcinogens and genotoxins is limited and based on measurement of maternal plasma concentrations or analysis of cord blood. Transplacental transfer of carcinogens in smoke and smoke-related damage to fetal tissue have been demonstrated, and the mycotoxin aflatoxin B1 or its metabolites have been detected in cord blood, as have metabolites of pesticides and polychlorinated biphenyls. New biomarkers may provide important information on the transplacental transfer of genotoxic compounds [37]. Individuals occupationally exposed to potential mutagens/carcinogens represent the most suitable groups for epidemiological studies aimed at assessing the risk for the individual or the offspring. Reproductive epidemiology has suggested a risk of spontaneous abortions or malformation in the offspring of workers exposed to chemicals in work environments, but data are often conflicting due to methodological problems. The statistical analysis data on the fertility and other reproductive end points in workers exposed to organic solvents show that the differences in the reproductive end points between the control and exposed groups were significant ($p < 0.05$) [38].

3.9. Impact on lactation or toxicants in breast milk

Transfer of toxic chemicals to breast milk represents an important, although not widely recognized, chemical exposure route for the infant [39]. For an increasing number of nursing mothers who resume their professional activities after giving birth, the obvious benefits of breastfeeding must be evaluated versus the risk of transfer of industrial chemicals to breast milk. Qualitative and quantitative reviews have been made of breast milk contaminants in lactating women and possible physiologically based pharmacokinetic models have been constructed in other studies to assess the risk for infants whose mothers were exposed to chemicals at work [40].

4. Discussion

Occupational diseases affect all organ systems and include pulmonary disease, musculoskeletal injuries, cancer, traumatic injuries, occupationally induced cardiovascular disease, reproductive illnesses, neurotoxic disorders, noise-induced hearing loss, dermatologic conditions, and psychological ailments. Most occupational diseases are clinically indistinguishable from nonoccupational illnesses in terms of etiologies. A diagnosis may be further complicated by a long latency period between occupational exposure to a toxicant and the onset of an illness. In addition to the dearth in information about workplace genotoxins (or teratogens), workers are frequently not informed about any known reproductive health hazards.

A medical history of occupational exposure to a toxicant is the primary tool for a diagnosis of work-related disease. Proper diagnosis of occupational disease permits proper treatment of the affected patient and also provides a basis for recognition of other similarly exposed workers who may also be at risk of toxic exposure. Replacing workplace genotoxins with relatively benign chemicals or instituting and implementing a comprehensive policy for safe handling of these compounds represents effective prevention measures. Other effective modes of prevention include ventilation, alteration in work practices, and use of personal protective equipment. Care for most of the patients with occupational diseases will therefore continue to be the responsibility of primary care physicians, and these physicians must become more highly attuned to the possibility that their patients may have diseases induced by toxic exposures encountered at work [41].

Many industries have adopted exclusionary policies whereby fertile women are refused work where there are known or suspected reproductive health hazards. Policies that allow workers to transfer to a different job while pregnant or while planning a child are viable alternative options. A pregnant or fertile worker should never have to stay in a job where she or her unborn child will be exposed to hazards because no other work is available to her [42]. Damme's study [43] included an evaluation of medical malpractice

cases involving standards of care within the context of occupational diseases. Although it is impossible to predict how the courts will rule in any given case, inferences can be drawn based on this preliminary analysis. For instance, it would be prudent for a healthcare professional to expand a clinical workup of a patient presenting with puzzling symptoms to include recording work experiences. The early diagnosis of work-related disease through inclusion of an occupational history could uncover community-wide/industry-wide reproductive health issues caused by genotoxins and facilitate the introduction of appropriate preventive measures [43].

4.1. New technologies to assess reproductive toxicants

Traditional animal study designs for assessing both reproductive and developmental toxicities cannot accommodate the evaluation of large numbers of chemicals and require the development of alternative technologies. The development of high-throughput techniques to analyze the genome, transcriptome, proteome, and metabolome is revolutionizing the way scientists and health professionals address the biological component of reproductive toxicology. From this information, it is now possible to establish relationships between metabolite levels and the cellular responses of any organism to chemical and/or nutritional stimuli that may be associated with one or more adverse effects or disease caused by the chemical [44]. Two of the most widely used platforms for metabolomics analyses are nuclear magnetic resonance and mass spectrometry. Nuclear magnetic resonance technology has been used to detect changes in metabolites following exposure to environmental or industrial toxicants. The future challenge for reproductive toxicologists in both the industrial and environmental settings is the integration of high-throughput technologies such as transcriptomics, proteomics, and metabolomics to prioritize the many thousands of industrial chemicals with little or no reproductive hazard information.

4.2. Global regulations and guidelines for reproductive health of workers

The upcoming European chemicals legislation Registration, Evaluation, and Authorisation of Chemicals (REACH) will require risk assessment of many thousands of chemicals. It is, therefore, necessary to develop intelligent testing strategies to ensure that chemicals of concern are identified, while minimizing the testing of chemicals used on animals. Xenobiotics may perturb the reproductive cycle, and for this reason, several reproductive studies are recommended under REACH [45]. Several toxicants with reported reproductive and developmental effects are still in regular commercial or therapeutic use and thus present potential exposure to workers. Progress has been limited in identifying hazards and quantifying their potencies and in separating the contributions of these hazards from other etiologic factors. Identifying the causative agents, mechanisms of action, and any potential target populations present the opportunity to intervene and protect the reproductive health of workers. Although many research challenges exist today, recent technological and methodological advances have been made that allow researchers to overcome some of these obstacles. If is recommended future directions in occupational reproductive health research, especially focused on reproductive toxic chemicals and physical stress. By bridging interdisciplinary gaps, the scientific community can work together to improve health and reduce adverse outcomes [46]. Occupational exposures can harm a developing child even after it is born. Babies and children are particularly vulnerable to the effects of workplace hazards, which may be brought into the home on clothing, shoes, skin, and hair. Risk assessment is an evolving process, based not only on toxicology, but also on a broad background of knowledge in fields ranging from chemistry to physiology and molecular biology and from environmental transport processes to applied statistics. Risk assessment procedures must be continually updated to reflect advances in these basic sciences. Occupational health and safety specialists must work with the scientific community at large to incorporate advances in the basic sciences into their extrapolations [47].

Because most chemicals in working environments have not been adequately studied for their possible effects on human health and reproduction, it is difficult to know exactly which ones will have negative effects on a worker's health. Therefore, both workers and employers should work together to eliminate hazardous exposures altogether or at least to reduce them to the levels permitted by national or internationally recognized standards. Employers should provide workers with adequate education about any potential hazards in the workplace. Much more work needs to be done to ensure the complete protection of all workers' reproductive health. Governments have the responsibility to take some actions toward protecting workers' reproductive health. Action required starts with making a national priority of promoting and supporting research on occupational causes of reproductive toxicity. Other public health actions include hazard surveillance and primary prevention activities such as reductions in the use of toxic materials, informed substitution, ventilation as well as protective equipment.

Conflicts of interest

The author has no potential conflicts of interest to report relevant to this article.

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