Chemical Research in Toxicology

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Review

What to Expect When Expecting in Lab: A Review of Unique Risks and Resources for Pregnant Researchers in the Chemical Laboratory

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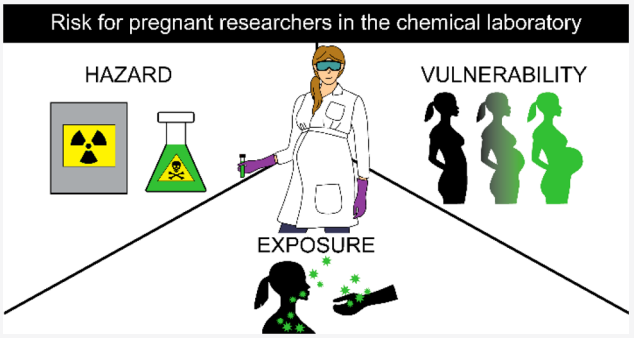
ABSTRACT: Pregnancy presents a unique risk to chemical researchers due to their occupational exposures to chemical, equipment, and physical hazards in chemical research laboratories across science, engineering, and technology disciplines. Understanding "risk" as a function of hazard, exposure, and vulnerability, this review aims to critically examine the state of the science for the risks and associated recommendations (or lack thereof) for pregnant researchers in chemical laboratories (labs). Commonly encountered hazards for pregnant lab workers include chemical hazards (organic solvents, heavy metals, engineered nanomaterials, and endocrine disruptors), radiation hazards (ionizing radiation producing equipment and materials and nonionizing radiation producing equipment), and other hazards related to the lab environment (excessive noise, excessive heat, psychosocial stress, strenuous physical work, and/or abnormal working hours). Lab relevant doses and routes of exposure in the chemical lab environment along with literature and governmental recommendations or resources for exposure mitigation are critically assessed. The specific windows of vulnerability based on stage of pregnancy are described for each hazard, if available. Finally, policy gaps for further scientific research are detailed to enhance future guidance to protect pregnant lab workers.



1. INTRODUCTION

There is substantial evidence showing that more diverse teams produce more innovative work and have higher citation rates.[1−4] Despite receiving approximately half of the science, technology, engineering, and math (STEM) baccalaureate degrees, women are increasingly underrepresented as career stages advance, with particularly high attrition in the midcareer—a time when many women have children.[3,5] For pregnant laboratory (lab) workers, one component of this "leaky pipeline" may result from uncertainty in the risks borne by pregnant researchers among other challenges related to childrearing while working in a research laboratory. This notion is supported by a 2019 study by Cech and Blair-Loy that showed 43% of female scientists left full-time STEM employment after the birth of their first child, as opposed to 23% of male first-time parent scientists and 24% of childless women scientists.[6]

While some organizations offer personalized risk assessments for pregnant researchers to inform the development of a safe work plan, this approach has limitations. First, pregnant researchers may not want to disclose their pregnancy until a later stage, leaving the task of identifying and assessing risks to the pregnant researcher themselves. Further, information on reproductive or developmental effects is scattered or opaque for many hazards encountered in a chemical lab setting, including information on permissible exposure levels and methods of gauging one's actual exposure. For example, the available resources often identify risks (e.g., "solvents") without much actionable information.[7] This may lead to unintentional exposures to hazardous substances during early pregnancy, which is often a more vulnerable time for miscarriages and birth defects. Further, when pregnant researchers are told that a hazard poses a "minimal" or "small" amount of risk (since it is very rare or unlikely to be able to say something poses "zero" risk), it still leaves a feeling of anxiety or uneasiness about their work.[8] Finally, this creates a situation where each individual is recreating a risk assessment rather than having the benefit of previous efforts to identify and characterize hazards of concern. As such, this review aims to review the potential risks for pregnant researchers in a chemical lab, where a chemical lab is defined as an industry or academic laboratory engaging in primary research in fields like chemistry, engineering, or medicine, but excluding biological work with substances such

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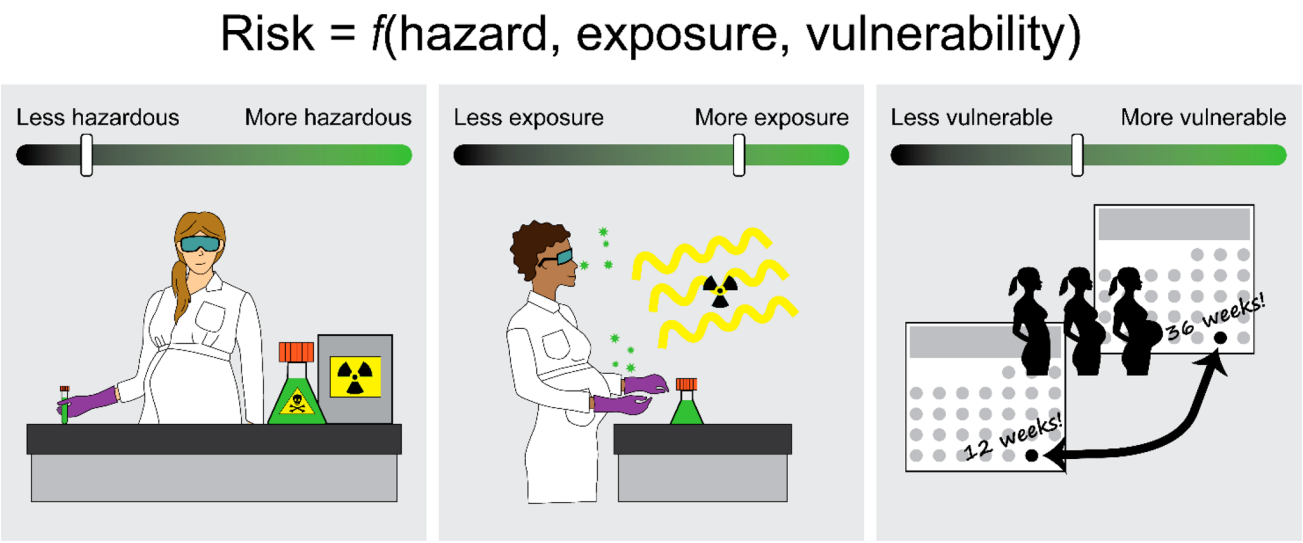

Figure 1. Risk associated with chemical laboratory work for pregnant researchers depends on the level of hazard, exposure, and vulnerability, where each exists on a scale that contributes to overall risk. Types of hazards in a chemical lab include chemical and radiation hazards, among others. Main routes of exposure are dermal, oral, and inhalation exposure, along with ambient exposure to hazardous environments such as radiation or sound. A pregnant researcher and their developing fetus can be more or less vulnerable to certain hazards and exposures based on the progression of their pregnancy.

Table 1. Adverse Effects and Outcomes Related to Hazards in Chemical Laboratories

Effect	Definition	Common outcomes
Reproductive effects	Adverse effects on adult male and female sexual function and fertility; also includes adverse effects on the development of the embryo/fetus.[16]	Encompasses birth outcomes and fetal, neonatal, and fertility effects.
Birth outcomes	Final result from a fertilization event (also called pregnancy outcomes).	Embryonal or fetal resorption (disintegration and assimilation of embryo/fetus in the uterus); spontaneous abortion or miscarriage; preterm birth; stillbirth.
Fetal effects	Adverse effects on fetal growth and organ or tissue development causing abnormalities (also called teratogenic effects).	Organ malformations; dysmorphogenesis (formation of abnormal tissue); cleft palate; intrauterine growth restriction; neural tube defects.
Neonatal (and beyond) effects	Adverse effects observed during the neonatal period, immediately after birth to 4 weeks of age, due to exposures in utero; also noted are any significant effects beyond 4 weeks of age into childhood.	Neonatal: Low birthweight; low Apgar score. Beyond: reduced IQ; behavioral problems; autism.
Fertility effects	Adverse effects on adult male and female sexual function and fertility (fecundity).	Infertility; low sperm count; prolonged time to pregnancy; irregular menstrual cycles.
Maternal effects	Adverse effects on the health of the mother (often via stressors) that may have secondary reproductive effects.	Elevated maternal body temperature; early uterine contractions; hypertension; gestational diabetes.

as pathogens or live organisms. By synthesizing and critically assessing the state of science of lab environment exposures and risks most relevant to embryonal/fetal development and pregnancy outcomes, this manuscript aims at providing resources to pregnant researchers as well as relevant organizations to inform risk management, mitigation, avoidance, and alternatives.

1.1. Risk for Pregnant Researchers. Risk can be expressed conceptually as the following function of three variables, known as "the risk equation":

$$\text{risk} = f(\text{hazard, exposure, vulnerability})$$

where hazard is an inherent property of the substance in question, exposure depends on the time, dose, and type of interaction with the substance, and vulnerability addresses unique timeframes when susceptibility is heightened or reduced (Figure 1).[9] Accordingly, an individual's overall risk can be reduced by minimizing any of the three variables by eliminating the intrinsic hazard by working with a safe chemical,[10] limiting exposure through appropriate control measures, or avoiding periods of increased vulnerability (e.g., pregnancy).

1.1.1. Hazard. Working in a chemical lab can include working with hazardous substances, resulting in associated risks for researchers, particularly those who are pregnant, upon exposure. Commonly encountered hazards include chemical hazards (e.g., organic solvents, heavy metals, engineered nanomaterials, and endocrine disruptors), radiation hazards (e.g., ionizing radiation producing equipment and materials and nonionizing radiation producing equipment), and other hazards related to the lab environment (e.g., excessive noise, excessive heat, psychosocial stress, strenuous physical work, and/or abnormal working hours). Each hazard, and preferably the confluence of the hazards, should be evaluated for the potential to initiate biochemical mechanisms of teratogenicity and other adverse effects. Reducing hazard is the most promising route to ensure low risk, as it is an intrinsic and constant property of chemicals and processes, whereas exposure control can fail and vulnerability is circumstantial.[11] This approach is one of the key pillars of green chemistry which aims to design safer chemicals, materials, and processes by reducing or eliminating the use of hazardous substances altogether.[10−12] Therefore, implementing green chemistry

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Chem. Res. Toxicol. 2022, 35, 163−198

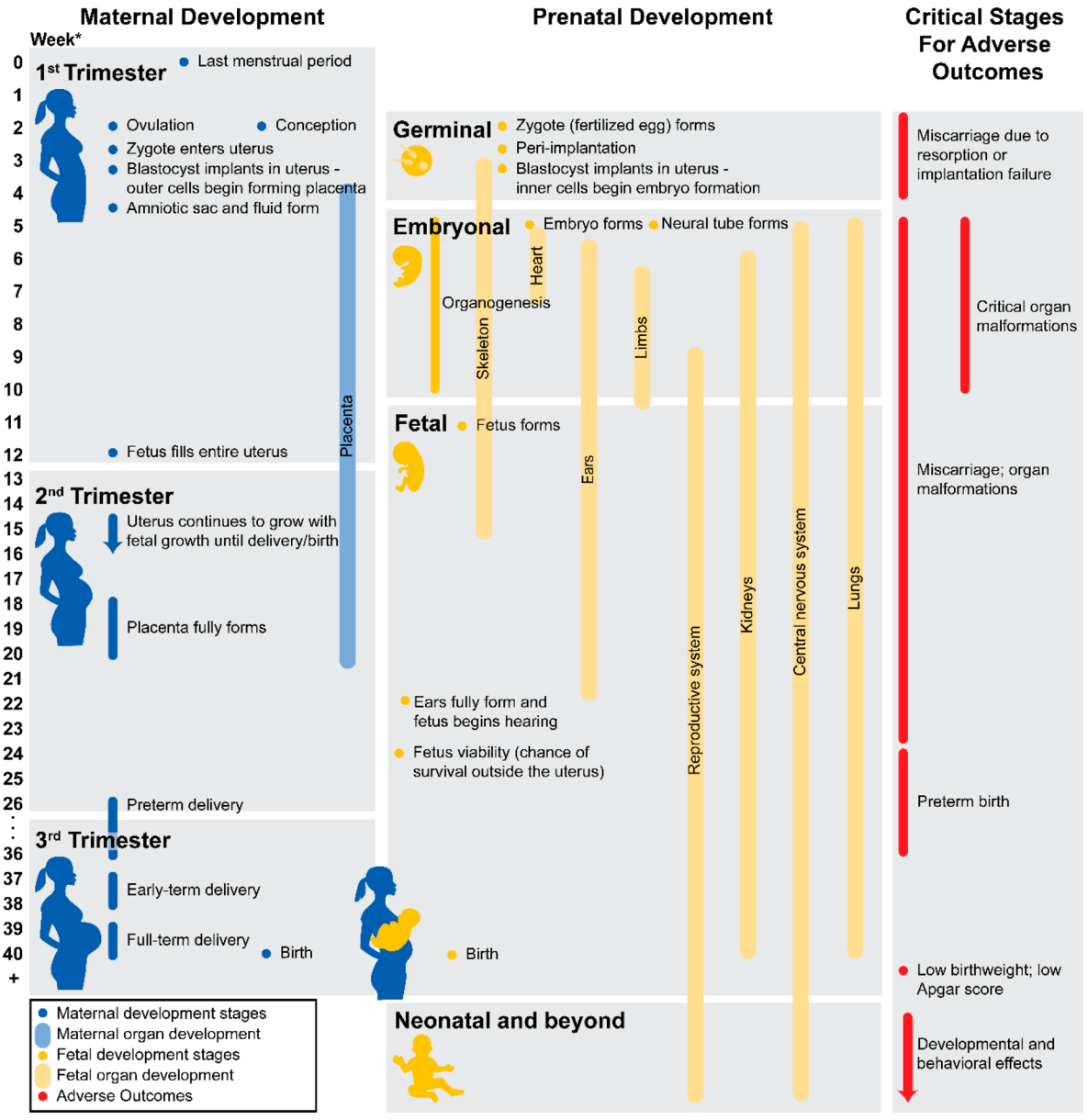

Figure 2. Important phases of maternal and prenatal development along with critical stages for when selected adverse outcomes can occur.[22−24] Note: The common convention to track pregnancies is to start from the date of the last menstrual period instead of the date of fertilization (which happens approximately 2 weeks later). The time in pregnancy is used instead of gestational age for ease of application and understanding of results, and any scientific studies that use gestational age will be adjusted by two weeks to follow time in pregnancy based on last menstrual period. Further, gestation in animal models is much shorter than human gestation, so equivalent time in pregnancy will be noted when discussing applicable results.[25]

practices would directly benefit pregnant researchers in a laboratory setting.

When examining hazards, numerous adverse effects related to reproduction and pregnancy emerge, which can be categorized into several adverse effects with common outcomes (Table 1). While some effects could fall into several categories (for example, low birth weight may be a birth outcome or a neonatal effect), the categories defined in Table 1 will be used. Additionally, while not focused on fertility effects, fertility is closely related to pregnancy and fetal development, meaning that effects on fertility (both male and female) are included when notable. Also, since it would be dangerous and unethical to perform medical studies of hazards directly involving pregnant women, the toxicological literature relies on observational human studies, in vitro human tissue studies, and animal model studies (most commonly mice and rats) to identify adverse effects. Animal studies are of great use in modeling the toxicity of hazards as they allow for precisely controlled studies permitting accurate determination of effects and thorough physical examinations both pre- and post-mortem.[13,14] While assessing the results from animal studies, it is important to note that these do not necessarily translate to humans due to limitations in detecting certain adverse effects in animal subjects, differences in receptor densities, unexpected human toxicities, and interspecies differences in absorption, distribution, metabolism, and excretion.[13−15] Knowing this, it is still common practice to convert doses in animal studies to appropriate human doses, regardless of exposure route, via

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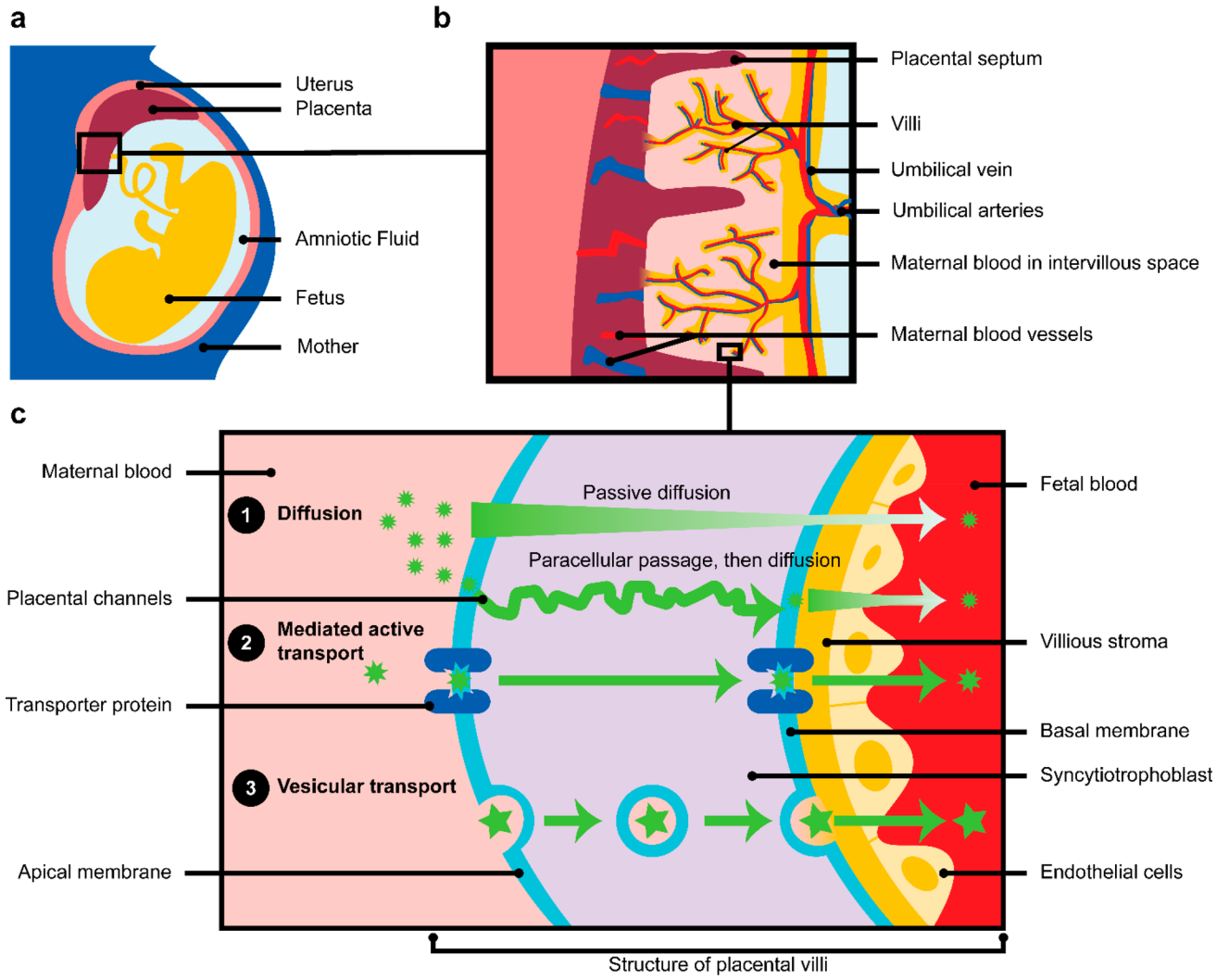

Figure 3. (a) Basic structure of fetal and maternal organs with (b) showing the structures within the placenta and (c) showing the structure of placental villi and the main mechanisms of transport across the placenta: (1) diffusion, (2) mediated active transport, and (3) vesicular transport.[31,32,34]

allometric scaling, a calculation based on the normalization of dose to body mass and surface area.[14] The conversion is most commonly applied by dividing animal "no observed adverse effect level" doses with an animal specific correction factor (e.g., 7.4 for mice, 6.2 for rats; other species available in literature)[14] into human equivalent doses (HEDs). Once the HED is calculated, a safety factor—with the accepted, default safety factor of 10—is included by dividing the HED by the safety factor to reach acceptable starting doses for human exposure where no effect is expected.[14]

1.1.2. Exposure. Laboratory exposures for researchers can be divided into chemical and nonchemical in nature. The three main routes of chemical exposure are oral, dermal, and inhalation.[17,18] Since chemical laboratories with standard safety procedures typically prohibit food or drink inside the lab and require the use of personal protective equipment (PPE), exposure via oral or dermal routes are anticipated to be minimal. Therefore, inhalation is expected to be the most relevant route of exposure followed by accidental dermal absorption, yet this ultimately depends on specific lab setups and materials used. Other nonchemical exposures include radiation and excessive noise or heat. In situations where hazards cannot be eliminated or substituted—the preferred approach—exposure can be moderated via engineering controls, administrative controls, and PPE controls, in order of decreasing effectiveness.[10] Engineering controls isolate researchers from hazards and include fume hoods, glove boxes, and the enclosing and shielding of radiation producing equipment. Administrative controls alter the procedures in place to become safer, such as changing work schedules or standard operating procedures. PPE is the final safety measure, which may include the use of respirators, special chemical-resistant gloves, and radiation-blocking lead aprons. Minimizing exposure for pregnant researchers may include several or all these controls, but hazard reduction should always be prioritized before exposure control measures are weighed.

Important to note, neonatal exposure of infants to both chemicals and radiation can also occur via breast milk stemming from maternal exposure.[19,20] This exposure route is important for breastfeeding researchers to consider. As such, effects from lactation exposure are included when notable but are not the focus of this review.

1.1.3. Vulnerability. Risks stemming from various hazards change over the course of a pregnancy, resulting in varying

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. Common Organic Solvents Encountered in a Chemical Laboratory with Corresponding CAS Number and Global Harmonization System Classification for Reproductive Toxicity and Adverse Reproductive Effects on Humans or Animals Based on Information from Toxicity Profiles in Online Databases[17,18,38−41] and Other Literature[a]

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
Acetic acid	64-19-7	N	BO	No discernible effects on fetal survival (mice, 16−345 mg/kg-day, oral).[17]
				Low numbers of spontaneous abortions (mice, 1600 mg/kg-day, oral).[17]
				No discernible effects on fetal survival (rats, 1600 mg/kg-day, oral).[17]
				No discernible effects on fetal survival (rabbits, 16−1600 mg/kg-day, oral).[17]
				No evidence of teratogenicity.[17]
			F	No significant abnormalities in either soft or skeletal tissues (mice, 15−345 mg/kg-day, oral).[17]
				Slight reductions in ossification (mice, 1600 mg/kg-day, oral).[17]
				No abnormalities (rats, 1600 mg/kg-day, oral).[17]
			FR	No evidence of reproductive toxicity.[17]
				No discernible effects on maternal survival (mice, rats, and rabbits, 16−1600 mg/kg-day, oral).[17]
			M	Slightly reduced bodyweight gain (mice, 16−1600 mg/kg-day, oral).[17]
				Dose-dependent decrease in maternal body weight attributable to bactericidal properties of acetic acid within the gastrointestinal tract of the rabbits (rabbits, > 74.3 mg/kg-day, oral).[17]
Acetone	67-64-1	2	BO	Slight increase in later resorptions (mice, 6600 ppm, inhalation).[44]
				No evidence of teratogenicity (chick embryos, 39 and 78 mg, yolk sac injection).[39]
			F	Decreased fetal body weight (mice, 6600 ppm, inhalation).[44]
				Reduced fetal body weight and fetal malformations at high doses (rats, 11000 ppm, inhalation).[44]
			N	Reduced postnatal pup survival (mice, 3500 mg/kg/day acetone on gestation days 6−10, oral).[18]
				Increased number of abnormal sperm (human occupation exposure, 69.6−94.5 ppm of acetone and styrene, inhalation).[45]
				Premature menstrual periods in 3 of 4 women (human, 1000 ppm for 7.5 h, inhalation).[39]
			FR	No observed lesions in female reproductive organs (mice, 0.2 mL painted on skin, dermal).[18]
				No effects on testes weight or testicular histopathology (rats, 5000 ppm, oral).[46]
				Decreased epididymal weights, depressed sperm motility, and increased abnormal sperm (rats, 3400 mg/kg-day, oral).[47]
			M	Significant decrease in maternal body weight (rats, 11000 ppm, inhalation).[44]
			BO	Increased resorptions and spontaneous abortions (rats, 1827 ppm, inhalation).[40]
				Increased spontaneous abortions and stillbirths (rabbits, 30 mg/kg, oral).[40]
				Reduced fetal body weight and 5 out of 9 litters developed skeletal disorders (hamsters, 8000 ppm, inhalation).[40]
			F	Increase in malformed offspring with rib fusions being most common (hamsters, 300−400 mg/kg, oral).[40]
				No effect on fetal weight and no significant difference in anomalies (rats, 1000−1827 ppm, inhalation).[40]
Acetonitrile (ACN or MeCN)	75-05-8	N	FR	No observed effects on fertility (rats, 100−1200 ppm, inhalation).[40]
				Reduced maternal body weight at lower doses and maternal mortality in 4 out of 12 dams at a higher dose (hamsters, 200−300 and 400 mg/kg respectively, oral).[40]
				Deaths in 2 out of 33 dams (rats, 1200 ppm, inhalation).[40]
			M	Mortality in 8 out of 20 dams as well as reduced maternal body weight (rats, 1827 ppm, inhalation).[40]
				Mortality in 2 dams, four emaciated dams out of 25 (rats, 275 mg/kg-day, oral).[40]
				Mortality in 1 out of 5 dams exposed to high concentrations. (rabbits, 30 mg/kg, oral).[40]
				Note: Acetonitrile can slowly convert to cyanide, and it is suspected that many of the dam deaths are attributable to cyanide release and not directly acetonitrile.
Anisole (methoxybenzene)	100-66-3	N	BO	No effect on birth outcomes (rats, 50−800 mg/kg-day, oral).[17]
			F	Lower fetal body weights, discolored skin, and moderate subcutaneous edema (rats, 800 mg/kg-day, oral).[17]
			M	Reduced maternal body weight gain and pregnant uterus weight (rats, 800 mg/kg-day, oral).[17]
Benzene	71-43-2	2	BO	Limited evidence of increased incidence of spontaneous abortion and intrauterine asphyxia of the fetus as compared to workers with no exposure or shorter exposure periods (chronic human occupational exposure, petroleum as the major source of benzene, inhalation).[18]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
N-butanol	71-36-3	N	F	Increase in abortions and resorptions (rabbits, 312 ppm, inhalation).[18]
				No effect on resorptions (mice, 500 ppm, inhalation; inhalation rats, 2000 ppm, inhalation; rabbits, 500 ppm, inhalation). [18]
				Delayed bone formation and bone marrow damage (multiple animal studies, inhalation).[41]
				Decreased body weight and delayed ossification (mice, 500 ppm, inhalation).[18]
				Reduced fetal weight and increased fetal anomalies (rabbits, 313 ppm, inhalation).[18]
				Reduced fetal body weight (mice, 1300 mg/kg-day, oral).[18]
			N	Low birth weight via maternal inhalation exposure (multiple animal studies, inhalation).[41]
			FR	Irregular menstrual periods and a decrease in ovary size (human occupational exposure, chronic exposure over months, inhalation).[48]
				Endometrial polyps and ovarian lesions in females and preputial gland lesions in males (mice, 600 mg/kg-day for 2 years, oral).[18]
				Bilateral cysts, testicular atrophy, decreased sperm count, increase in abnormal sperm (mice, 300 ppm, inhalation).[18]
			BO	No adverse reproductive effects (rats, 1000 mg/kg-day, oral).[18]
				No effect on resorption or fetal viability (rats, 3500−8000 ppm, inhalation).[40]
				Pre- and postimplantation losses and spontaneous abortions, (rats, 1300 mg/kg-day, oral).[40]
				Reduced crown-rump length and increased malformations (rats, 0.24−4%, oral).[40]
			F	Decreased fetal body weight (rats, 5654 mg/kg-day, oral).[40]
				Skeletal variations and thymic remnant in the neck (rats, 0.2−5.0%, oral).[40]
				Reduced fetal body weight and increased abnormal skeletal and visceral malformations (rats, 6000−8000 ppm, inhalation).[40]
			FR	No differences in estrous cycle and no changes in relative organ weights (rats, 0.24−4%, oral).[40]
				Decreased fertility (rats, 1300 mg/kg-day, oral).[40]
			M	Decreased maternal body weight and food consumption (rats, 0.2−5.0%, oral).[40]
				Maternal fatalities in 2 out of 18 dams and lower food consumption (rats, 3500−8000 ppm, inhalation).[40]
			BO	Fetal resorption and decreased conception rates (mice, 100 ppm, inhalation).[18]
				Spontaneous abortions (mice and rats, 30−300 ppm, inhalation).[18]
				Increased fetal resorptions (rats, 30 ppm, inhalation).[18]
				Spontaneous abortions (rabbits, 63 mg/kg-day, oral).[18]
Chloroform	67-66-3	2	F	80% higher risk of intrauterine growth retardation at higher dose and 30% higher risk at lower doses as compared undetectable levels of chloroform (human study of 688 subjects exposed to chloroform in drinking water as a byproduct of chlorine treatment, ≥10 ug/L and 1−9 ug/L, oral).[18]
				Cleft palate, decreased ossifications, and decreased crown-rump length (mice, 100 ppm during organogenesis, inhalation).[18]
				Delayed ossification and wavy ribs at 30 ppm, imperforate anus and missing ribs at 100 ppm, decreased fetal body weight and crown-rump length at 300 ppm (rats, 30−300 ppm, inhalation).
			N	30% higher risk of low birth weight as compared to undetectable levels of chloroform (human study of 688 subjects exposed to chloroform in drinking water as a byproduct of chlorine treatment, ≥10 ug/L, oral).[18]
				Hepatocellular degradation (mice, 41 mg/kg while in utero, during lactation, and into adulthood, oral).[49]
			FR	Abnormal sperm (mice, 400 ppm over 5 days, inhalation).[18]
				Gonadal atrophy (rats, 410 mg/kg/day, oral). [50]
			M	Decreased maternal body weight (rats, 150 mg/m^3, inhalation).[49]
			BO	No evidence of effects on resorption frequency or pre- or postimplantation loss (rats, 100−1000 mg/kg-day, oral).[51]
				No adverse effects on viable fetuses or number of implantations (rats, 1000−10000 ppm, inhalation).[51]
				No differences in fetal body weight (rats, 250−1000 mg/kg-day, oral).[51]
Cyclohexane	110-82-7	N	F	No evidence of variations or malformations (rats, 100−1000 mg/kg-day, oral).[51]
				No evidence of developmental toxicity (rats, 7000 ppm, inhalation).[40]
				No observed developmental effects (rabbits, 500−7000 ppm cyclohexane, inhalation).[17]
			N	Reduced pup weight through lactation period, gestational and lactation exposure (rats, 7000 ppm, inhalation).[17]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
			FR	No observed effects on reproductive function (rats, 500−7000 ppm, inhalation).[17]
			M	No significant body weight changes and no changes in food consumption or uterine weights (rats, 100−1000 mg/kg-day, oral).[51]
				Decreased reaction to sound stimulus (rats, 2000 and 7000 ppm, inhalation).[17,40]
				Reduced maternal weight gain (rats, 7000 ppm, inhalation).[17,40]
				No maternal effects observed (rabbits, 500−7000 ppm, inhalation).[17]
Decane	124-18-5	N	−	No evidence of adverse outcomes, very limited amount of studies available.[17,51]
1,2-Dichloroethene (1,2-DCE)	156-59-2	N	BO	Resorption rates not statistically significant (rats, 6000 and 12000 ppm of trans-1,2-DCE, inhalation).[18,39]
			F	Reduced fetal mean weights due to reduced maternal food consumption rather than gestational exposure (rats, 12000 ppm of trans-1,2-DCE, inhalation).[18]
			FR	No lesions in mammary glands, clitoral glands, ovaries, uterus, seminal vesicles, prostate, testes or preputial glands (rats, 1900 mg/kg/day of cis-1,2-DCE, oral).[18]
				No histopathological lesions in reproductive organs (rats, trans-1,2-DCE).[18]
				No organ weight changes or gross lesions in reproductive organs over the course of a 14-week exposure study (mice and rats, doses from 190−8065 mg/kg-day of trans-1,2-DCE, oral).[40]
			M	Reduced maternal body weight (rats, 3134, 5778, and 6906 mg/kg-day of a 1,2-DCE isomer mixture, oral).[40]
Dichloromethane (DCM)	75-09-2	2	BO	No adverse birth outcomes observed (rats, 1500 ppm for two generations, inhalation).[18,40,52]
			F	Abnormal ossification (mice and rats, 1250 ppm during gestation days 6−15, inhalation).[40]
				Decreased fetal body weight (rats, 4500 ppm, inhalation).
			N	No observed, statistically significant impacts on neonatal survival and some behavioral effects (rats, 4500 ppm, inhalation).[40]
Diethyl ether	60-29-7	2	FR	No effects on male fertility index in 8 out of 9 studies (mice, 150 and 200 ppm, inhalation).[40]
			M	Increased percentage of hemoglobin in maternal blood indicating rupturing of red blood cells or CO poisoning (mice and rats, 1250 ppm, inhalation).[40]
			BO	Limited evidence that chronic exposure leads to spontaneous abortions, 18 out of 31 pregnancies ended in spontaneous abortion (human occupational exposure, anesthesiologists exposed to ethyl ether and other agents, 25 h a week, inhalation).[53]
				96% of embryos died (chick embryos, 20 vol% of vaporized ethyl ether for 6 h for 3 days, in vivo).[53]
				Increase in resorptions (mice, 65000−73000 ppm during organogenesis, inhalation).[51]
			F	Decreased head growth and increased skeletal variations resulting (mice, 20 min increments during pregnancy).[51]
			N	No effects on cephalic diameter, body weight, or viability, no delay in cerebellar maturation of newborn pups (rats, 10 min increments during pregnancy, inhalation).[51]
Dimethoxymethane	109-87-5	N		No adverse effects have been observed on spermatozoa (mice, 49280 or 9856 mg/m^3, inhalation).[53]
			FR	Effects on male fertility including 30% reduction in adult, daily sperm production and germ cells in the testes (rats, neonatal exposure from soaked cotton pad, inhalation).[51]
			BO	Increase in resorptions and postimplantation loss (rabbits, 300 and 1000 mg/kg-day, oral).[17]
			FR	No adverse effects observed in male and female reproductive organs (rats, 0−9652 ppm, inhalation).[54]
			M	Symptoms of narcosis and reduced body weight (rats, 10068 ppm, inhalation).[54]
				Greater weight loss and lower food consumption (rabbits, 1000 mg/kg-day, oral).[17]
Dimethyl carbonate (DMC)	616-38-6	N	BO	Increased resorptions (mice, 3000 ppm, inhalation).[55]
				Reduced fetal body weight (mice, 3000 ppm, inhalation).[55]
			F	Cleft palate and malformations of skull and bones (mice, 3000 ppm, inhalation).[55]
				No adverse developmental effects observed (rats, 500 mg/kg, oral).[17]
			M	Reduced maternal body weight (mice, 3000 ppm, inhalation).[55]
				No maternal or fetal toxic effects (rabbits, 100−1000 mg/kg, oral).[17]
Dimethyl ether	115-10-6	N	F	Decreased fetal body weight and increased skeletal variation (rats, 40000 ppm, inhalation).[17]
				Excess ossification in the lumbar area (rats, 5000 ppm, inhalation).[17]
			FR	No effect on male or female reproductive organs (rats, 0.2−2.5%, inhalation).[17]
			M	Reduced maternal weight gain and loss of hearing (rats, 40000 ppm, inhalation).[17]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
Dimethyl sulfoxide (DMSO)	67-68-5	N	F	Percentage of embryonic abnormalities increased with increased dose (88% of embryos were abnormal with a 4% concentration) (mice, 0.04%-4%, dermal).[56]
				Decreases in fetal body weight (rats, 5000 mg/kg-day, oral).[17,56]
				Delayed ossification of the ribs (rats, 5000 mg/kg-day, oral).[17,56]
				No teratogenic effects observed (rabbits, 5 g/kg of 50% DMSO, oral).[17,56]
			M	Reduced weight gain and food consumption (rats, 5000 mg/kg-day, oral).[17,56]
			BO	Increased rate of spontaneous abortions (human occupational exposure, DMF mixed with other chemicals, inhalation).[41]
				Reduced implantation efficiency (rats, 32 ppm, inhalation).[41]
				Spontaneous abortions in 12 out of 12 dams (rats, 500 mg/m^3, inhalation).[41]
Dimethylformamide (DMF)	68-12-2	1B		Reduced number of viable fetuses produced by exposed males and unexposed females (rats, 30 ppm, inhalation).[49]
				Significantly reduced fetal weight (rats, 172 ppm, inhalation)
			F	Fetotoxic effects at maternally toxic concentrations (rats, 100 mg/kg, gastrostomy feeding tube).[49]
				Reduced fetal weight and increased malformations of live fetuses (rabbits, 188.9 mg/kg/day, oral).[41]
				Fetal malformations (rabbits, 450 ppm, inhalation).[49]
			N	Reduced live pup weight in second generation (mice, 1000−7000 mg/L, oral via drinking water).[49]
				No effects on semen volume, sperm motility, count, and morphology (monkeys, 500 ppm, inhalation).[49]
			FR	Reduced fertility and fecundity (mice, 4000 and 7000 mg/L, oral).[49]
				No effects on sperm density, motility, or sperm count (mice and rats, < 800 ppm, inhalation).[49]
			M	Maternal weight gain (rats, 300 ppm, inhalation).[49]
			BO	Spontaneous abortions, premature births, and low birth weights (human occupational exposure, 1,4-dioxane mixed with other chemicals, inhalation).[18]
1,4-Dioxane	123-91-1	N	F	One study observed reduced fetal weight and reduced sternum ossification (rats, 258−1033 mg, oral).[18]
			FR	No adverse effects observed in primary and secondary reproductive organs (rats, 3200 ppm for 13 weeks, 111 ppm for 2 years, and 1250 ppm for 2 years, inhalation).[18]
				No histological alterations in reproductive organs (mice and rats, 1614 and 2699 mg/kg-day for 13 weeks, 429 and 964 for 2 years, 1599 for 2 years, oral).[18]
Diphenyl ether	101-84-8	N	–	No studies on reproductive or developmental toxicity via pure diphenyl ether.[51] Instead, Therminol VP-1, a heat transfer fluid that is a mixture of diphenyl ether and biphenyl, can be used as a reproductive and developmental toxicity indicator.[51]
			F	No observed malformations resulting from gestational exposure (rats, 50−500 mg/kg-day, Therminol VP-1, oral).[17]
			M	Reduced mean weight gain, alopecia, and fur staining (rats, 200 and 500 mg/kg-day, Therminol VP-1, oral).[17]
				Maternal fatality rate of 8.3% (rats, 500 mg/kg-day, Therminol VP-1, oral).[17]
Ethanethiol	75-08-1	N	F	No studies available on reproductive or developmental effects.[18,57] Limited studies show evidence of adverse fetal effects of 2-methylpropane-2-thiol and butane-1-thiol, which can be used as reproductive and developmental toxicity indicators.[17]
Ethanol	64-17-5	2		Increased risk of spontaneous abortion (up to 5 times more likely) with consumption of 5+ alcoholic drinks per week (human study of 330 women in Denmark that had experienced spontaneous abortions, oral).[58]
			BO	Increase in spontaneous abortion (monkeys, ≥1.8 g/kg, oral).[59]
				Increased resorption of litters and fetal death (mice, 5 g/kg-day, oral; mice, 30% calories derived from ethanol, oral).[17,60]
				No effect on pregnancy outcomes (rats, 16000 ppm, inhalation).[61]
				Increased resorptions (rabbits, 15%, oral).[62]
				The United States Surgeon General states, "No amount of alcohol consumption can be considered safe during pregnancy. Alcohol consumption during pregnancy increases the risks of fetal birth defects, growth deficiencies, facial abnormalities, and the impairment of the fetal nervous system".[63]
			F	No incidences of external, visceral, or skeletal malformations (rats, 10000−20000 ppm, inhalation).[59]
				Increased fetal malformations such as skeletal, neurological, urogenital, and cardiovascular anomalies (mice, 30% calories derived from ethanol, oral).[60]
				Reduced fetal body weights (rats, 16000−20000 ppm, inhalation).[60]
			N	Reduced birth weight (human study of 8448 pregnancies with continuous interviews to track alcohol consumption, > 120g/week, oral).[59]
				Cognitive issues and behavior problems in children (human meta-analysis of over 10000 children whose mothers drank alcohol moderately or binged, oral).[63]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
				Decreased mental development at 8 months postnatal (human, 60 g/day, oral).[59]
				Facial dysmorphology and behavioral abnormalities (monkeys, ≥1.8 g/kg, oral).[59]
				No significant effects on pup growth or survival (mice, 2.2−7.8 g/kg-day, oral).[60]
				Reduced live pup weight (mice, 5−15%, oral).[17]
				No effects on postnatal neuromotor coordination, activity levels, and learning ability (rats, 16000 ppm, inhalation).[59]
			FR	Reduced sperm motility (mice, 16 g/kg-day, oral; mice, 5−15%, oral).[17,60]
				Maternal lethality (mice, 3600−7800 mg/kg-day, oral).[17]
			M	Severe maternal effects such as narcosis and decreased food consumption at high doses (rats, 20000 ppm, inhalation).[60]
				Reduced liquid intake and maternal body weight (rabbits, 15%, oral).[17]
			–	No studies on developmental toxicity available and few studies on reproductive toxicity.[51,61] The rapid hydrolysis of ethyl acetate to ethanol and acetic acid enables using those as developmental toxicity indicators.[17]
Ethyl acetate	141-78-6	N		No effects on sperm counts, motility, or sperm concentration (rats, 350−6000 ppm chronic exposure to ethyl acetate, inhalation).[17]
			FR	Adverse effects on plasma testosterone levels and sperm counts (rats, 16000 ppm for 5 min twice a day to ethyl acetate, inhalation).[17]
				No observed effects on number of implantations, resorption sites, and fetal viability (mice, 750−3000 mg/kg-day, oral).[49]
			BO	Reduction in live implantations observed (mice, 250−2500 mg/kg-day, oral).[49]
				No effects observed on resorption frequency or preimplantation loss (rats, 1000 mg/kg-day, oral).[49]
				Skeletal variations (mice, 2505 mg/m^3, inhalation).[49]
				Decreased pup body weight (mice, ≥840 mg/kg-day, oral).[49]
				Poorly ossified skull bone and unossified intermedia phalanges of the hindlimb (mice, 3500 mg/kg, dermal).[49]
			F	Poorly ossified and unossified vertebral centra (rats, 1000 mg/kg-day, oral).[41,49]
Ethylene glycol	107-21-1	2		Reduced fetal body weight, reduced skeletal ossification, malformations in skeleton (rats, > 1,000 mg/kg-day, oral).[49]
				Skeletal, external, and visceral malformations (rats, 2500 mg/kg, oral).[49]
				No observed developmental effects (rabbits, 100−2000 mg/kg-day, oral).
				More studies available.[18]
			FR	No observed adverse effects on reproductive organs (mice, 250−2500 mg/kg-day, oral).[49]
				No evidence of maternal toxicity (rats, 1000 mg/kg-day).[49]
			M	Increase in kidney weight, indicating maternal toxicity, along with reduced food consumption and maternal body weight (rats, 2500 mg/kg-day, oral).[49]
				Maternal mortality and degenerative changes in the kidney (rabbits, 2000 mg/kg-day, oral).[49]
				No studies regarding reproductive or developmental toxicity are available.[17,51]
Heptane	142-82-5	N	–	The European Chemicals Agency notes that hexane may be used as an indicator for the reproductive toxicity potential of heptane as it is structurally similar.[17]
				Increased spontaneous abortions and increased resorptions (mice, rats, 200−5000 ppm, inhalation).[18]
			BO	No effects on implantations or resorptions per litter (rats, 200−5000 ppm, inhalation).[18]
				Reduced fetal weight, more extreme in males (mice, 200−5000 ppm, inhalation).[18]
				Adverse effects on ossification (mice, 9017 ppm, inhalation).[18]
			F	At levels of maternal toxicity, fetal weight was reduced but no malformations occurred (mice, 7920 and 9900 mg/kg-day, oral).[18]
				No significant adverse developmental effects including no observed differences in fetal body weight and malformation incidents (rats, 200−9017 ppm, inhalation).[17,18]
Hexane	110-54-3	2		
			N	Reduced body weight in pups and delayed histogenesis of cerebellar cortex (rats, 500 ppm, inhalation).[18]
				No changes in sperm morphology (mice, 5000 ppm, up to 5 days, inhalation).[18]
				No reproductive lesions and no adverse effects observed (mice, 1000 and 10000 ppm for 13 weeks, inhalation).[18]
			FR	Testicular damage and degeneration of male fertility indicators with adverse effects worsening with longer exposure time (rats, 5000 ppm, inhalation; rats, 5000 ppm up to 6 weeks, inhalation; rats, 1000 ppm for 28 or 61 days, inhalation).[18,41]
				No reproductive effects (rats, 500 ppm for 6 months, inhalation).[18]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
			M	Reduced body and prostate weight in males (rats, 2000−1000 mg/kg-day oral).[18]
				Decrease in maternal body weight and pregnant uterine weight (mice, 5000 ppm, inhalation).[18]
				Maternal fatalities in 5 out of 33 dams (mice, 9900 mg/kg-day, oral).[18]
				No maternal fatalities, reduced weight gain at 5000 ppm (rats, 200−5000 ppm, inhalation).[18]
				Reduced weight gain during exposure period (rats, 3025 and 9017 ppm, inhalation).[17,18]
Isobutanol	78-83-1	N	–	No studies available on reproductive or developmental toxicity. As an isomer of isobutanol, n-butanol can be used for reproductive and developmental toxicity indicators.[64]
Isopropyl Acetate	108-21-4	N	–	No studies available on reproductive or developmental toxicity. The rapid hydrolysis of isopropyl acetate to isopropanol and acetic acid enables using those as reproductive and developmental toxicity indicators.[17]
			BO	Failure of implantation and increased resorption (rats, 7000 and 10000 ppm, inhalation).[17]
				No spontaneous abortions, implantation loss, resorption, or variable pregnancy duration (rabbits, 120−480 mg/kg-day, oral).[17]
				No external, skeletal, or visceral malformations, gestational exposure (rabbits, 120−480 mg/kg-day, oral).[17]
			F	Reduced fetal body weight (rats, 7000 and 10000 ppm, inhalation; rats, 800 and 1200 mg/kg-day, oral; rats, 1242 and 1605 mg/kg-day, oral).[17]
				Abnormal skeletal variations (rats, 1242 and 1605 mg/kg-day, oral).[17]
				Evidence of increased pup mortality (rats, 1000 mg/kg-day, oral).[17]
Isopropyl alcohol (IPA, isopropanol)	67-63-0	2	N	High number of offspring deaths in second generation after parental exposure, possibly due to underdeveloped metabolism in young (rats, 1000 mg/kg-day isopropanol, oral).[17]
			FR	No reproductive toxicity (rats, < 1000 mg/kg, oral).[17]
				Parental toxicity indicated by body, liver and kidney weight effects (rats, 1000 mg/kg-day, oral).[17]
				Reduced food and water intake, reduced body weight gain, increase in organ weights (rats, 0.5−2.0%, oral).[17]
			M	Small increase in maternal mortality and reduced weight gain (rats, 400−1200 mg/kg-day, oral).[17]
				Narcotic effects, reduced body weight gain, and reduced food intake (rats, 7000 and 10000 ppm, inhalation).[17]
				Reduced weight gain, clinical signs of intoxication, mortality at highest dose (rabbits, 120−480 mg/kg-day, oral).[17]
			BO	No adverse effects on fetal viability or survival (rats, 1.2−30 mg/kg, oral).[17,51]
Lactonitrile	78-97-7	2	F	No effects on fetal body weight and no abnormalities (rats, 1.2−30 mg/kg, oral).[17,51]
			FR	No effects on mating, fertility, and estrus cycle but some mating behavioral alterations observed at high doses (rats, 1.2−30 mg/kg, oral).[17,51]
			–	Limited information (one study) for isolated mesitylene. The C9 distillation fraction from petroleum processing contains mesitylene and other trimethylbenzene isomers (TMBs in C9 fraction) which can be used as reproductive and developmental toxicity indicators. [40]
			BO	Increase in fetal death, postimplantation loss (mice, 4059 mg/m3 TMBs in C9 fraction, inhalation).[40]
				Decreased live births and decreased litter sizes in second generation (rats, 271−4059 mg/m^3 TMBs in C9 fraction, inhalation).[40]
				No adverse effects on fetal viability, skeletal, visceral, or external morphology (rats, 5904 mg/m^3, inhalation).[40]
			F	Decreased fetal body weight (rats, 492−5904 mg/m^3, inhalation).[40]
				Cleft palate and unossified sternebrae and reduced fetal body weights (mice, 1353−4059 mg/m^3 TMBs in C9 fraction, inhalation).[40]
Mesitylene (1,3,5-trimethylbenzene)	108-67-8	N		Decreases in postnatal body weights occurred at lower doses each generation (rats, 271−4059 mg/m^3 TMBs in C9 fraction, inhalation).[40]
			N	Decreased pup survival (rats, 4059 mg/m^3 TMBs in C9 fraction,, inhalation).[40]
			FR	No lesions in reproductive organs and no alteration in fertility (rats, 271−4059 mg/m^3 TMBs in C9 fraction, inhalation).[40]
				Decreased male fertility in second generation (rats, 271−4059 mg/m^3 TMBs in C9 fraction, inhalation).[40]
				Decreased maternal body weight gain (rats, 492−5904 mg/m^3, inhalation).[40]
			M	Reduced body weight gain and decreased food consumption (rats, ≥1476 mg/m^3 and 2952 mg/m^3, inhalation).[40]
				Maternal fatality of 44% of dams and decreased body weight gain (mice, 4059 mg/m^3 TMBs in C9 fraction, inhalation).[40]
			BO	Decrease in number of live pups at lower dose and increase in fully resorbed litters at higher dose (mice, ≥7500 ppm and ≥10000 ppm, inhalation).[65]
Methanol	67-56-1	2		Increased late resorptions and reduced live fetuses (rats, 5000 ppm, inhalation).[65]
			F	No observed developmental effects (human case study, a pregnant woman ingested 250−500 mL in 38th week of pregnancy).[65]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
				Skeletal and visceral malformations (mice, 2000 ppm, inhalation). [65]
				Reduced fetal body weights, delayed ossification, skeletal anomalies, and cleft palate exencephaly (mice, 5000−15000 ppm, inhalation).[65]
				Reduction in fetal weight (rats, 10000 and 20000 ppm, inhalation).[65]
				Skeletal or visceral malformations (rats, 20000 ppm, inhalation).[65]
			N	Decreased organ weight (rats, 5000 ppm, inhalation).[65]
				Additional studies on postnatal development are available.[65]
			FR	No effects on menstrual cycles or conception (primates, 200−1800 ppm).[65,66]
				No adverse reproductive effects (rats, 800 ppm, inhalation).[65]
			M	Reduced body weight and reduced food and water intake (rats, 5000 ppm, inhalation).[65]
				Spontaneous abortion in 8 out of 8 pregnancies (macaques, 36 mg/kg-day, oral).[51]
				Decreases in live pups, pup viability, and pup body weights (rats, 0.03% by volume, orally in drinking water).[51]
			BO	Significant number of fetuses resorbed (rats, 0.006−0.5% volume, oral).[51]
				All fetuses resorbed (rats, 30−300 ppm, inhalation).[51]
				No live pups born (mice, 1000 mg/kg-day, oral).[51]
				Organ malformations and dysmorphogensis (mice, 125−250 mg/kg-day, gestational).[51]
				Reduced fetal body weights (rats, 16−620 mg/kg-day, diet).[51]
				Cardiovascular malformations (rats, 50 mg/kg-day, oral).[51]
2-Methoxyethanol	109-86-4	1B	F	Limb-bud dysmorphogensis (rats, 50−250 mg/kg-day, oral).[51]
				Reduced fetal body weight, cardiac malformations, skeletal malformations (rats, 50−100 ppm, inhalation).[51]
				Delayed ossification of vertebral centra and lumbar spurs (rats, 50 ppm, gestational inhalation).[51]
				Shortened or missing digits and other malformations (rabbits, 50 ppm, inhalation).[51]
			N	Limited neonatal data due to high embryo lethality.[51]
				Reduction in testes weights and the degeneration of sperm (rats, 500 and ≥100 mg/kg-day respectively, oral).[51]
			FR	Decreased sperm concentrations, sperm motility, increased abnormal sperm (rats, 0.1% concentration in drinking water, oral).[51]
				Decreased testicular size and atrophy of the seminiferous tubules (rats, 300 ppm, inhalation).[51]
			M	Anorexia and maternal body-weight loss, severe loss of appetite (macaques, 12−36 mg/kg-day, oral).[51]
Methyl acetate	79-20-9	N	–	No studies on reproductive or developmental toxicity available.[51,67] The rapid hydrolysis of methyl acetate to methanol and acetic acid enables using those as reproductive and developmental toxicity indicators.[17]
				Increased number of nonviable implantations and late resorptions (mice, 8000 ppm, inhalation).[18]
				Decrease number of viable implantations and increase in late resorptions (mice, 8000 ppm, inhalation).[41]
			BO	No effects on the number of uterine implantations, resorption, or live fetuses (mice and rats, ≤ 2500 ppm, inhalation).[18]
				No effects on resorption percentage or fetal viability (rats, ≤ 2500 ppm, inhalation).[18]
				No effects on early or late resorption or stillbirths (rabbits, ≤ 8000 ppm, inhalation).[18]
				Skeletal malformations (mice, 8000 ppm, inhalation).[41]
Methyl *tert*-butyl ether (TBME, MTBE)	1634-04-04	N		No effects on crown-rump distances, external malformations, or soft-tissue malformations (mice, 250−2500 ppm, inhalation).[18]
			F	Slight increase in fused sternebrae (mice, 250−2500 ppm, inhalation).[18]
				Reduced skeletal ossification and reduced body weight (mice, 4000 ppm, inhalation).
				Reduced fetal body weight, increase in cleft palate and skeletal malformations, reduction in partial fetal atelectasis(mice, 8000 ppm, inhalation).[18]
			N	Reduced pup viability and reduced pup body weight gain (rats, 1240 ppm and 2980 ppm, inhalation).[41]
				Reduced body weight (rats, 3000 ppm and 8000 ppm, inhalation).[41]
			FR	No gross lesions in the reproductive organs, no changes in testicular weight (mice and rabbits, ≤ 8000 ppm, inhalation).[18]
				No histological changes in the reproductive system (rats, ≤ 3000 ppm, inhalation).[18]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
				No structural effects on reproductive systems or performance (rats, 250−2500 ppm, inhalation).[18]
				No treatment-related lesions (rats, 400−8000, inhalation).[18]
				No effects on testicular or ovarian weights, no evidence of lesions (rats, 357−1428 mg/kg-day, oral).[18]
				No effects on germ cell frequency in testes and ovaries (rats, ≤ 1000 mg/kg-day, oral).[18]
				No lesions of the prostate, uterus, gonads but slight increase in testicular tumors in high-dose males (rats, 250 or 1000 mg/kg-day, 104 week exposure, oral). [18]
			M	Reduced body weight gain, reduced food consumption, and clinical signs of central nervous system depression (mice, 8000 ppm, inhalation).[18]
				Decrease in uterine weights (mice and rabbits, ≤ 8000 ppm, inhalation).[18]
2-Methyltetrahydrofuran (2-MeTHF)	96-47-9	N	BO	Insufficient studies available on reproductive and developmental toxicity.[64,68]
				Acute embryo toxicity (zebrafish, 2980 mg/L, in vivo).[68]
				Preimplantation loss (rats, 0.68 mg/L, inhalation).[69]
			BO	Increased resorptions (rats, ≥750 mg/kg, dermal).[69]
				Large number of resorptions including 24 out of 29 dams showed complete resorption (rats, 997 mg/kg-day, oral).[70]
				Decreased fetal body weight (rats, 0.478 mg/L, inhalation).[69]
				Delayed ossification (rats, 0.68 mg/L, inhalation).[69]
			F	Decreased body weight, incomplete closing of the skull, reduced or incomplete hyoid bone, and incomplete ossification of vertebrae (rats, ≥750 mg/kg, dermal).[69]
				Decreased fetal weight and increase in fetal stunted growth (rats, 400 mg/kg, oral).[69]
				No teratogenicity during postimplantation phase (rats, 124−494 mg/m^3, inhalation).[70]
				Decrease in pup survival (rats, 500 mg/kg-day, oral).[70]
N-Methyl-2-pyrrolidone (NMP)	872-50-4	1B	N	Decrease in pups surviving lactation and low body weights in second generation offspring (rats, mg/kg-day, oral).[70]
				Neurobehavioral effects in pups including latency, impairment in operant behavior with delayed spatial alteration (rats, 0.622 mg/L, inhalation).[69]
				Testicular effects observed (rats, 2060 mg/kg-day or 3 mg/L for 13 weeks, oral and inhalation).[69]
			FR	No testicular effects (rats, 0.618 mg/L for 90 days, inhalation; rats, 0.04−0.478 mg/L, inhalation).[69]
				Significant decreases in the male fertility index and female fecundity index (rats, 50−500 mg/kg-day, oral).[70]
				Depressed body weight gain (rats, 400 mg/kg, oral).[70]
			M	Reduced maternal body and placental weights (rats, 997 mg/kg-day, oral).[70]
				Prolonged clotting time and increased liver weight (rabbits, 1000 and 2000 mg/m^3, inhalation).[70]
				Decreased food intake and weight gain (rabbits, 175 and 540 mg/kg-day, oral).[70]
			−	Xylene is often present as a mix of isomers (mixed xylenes) including *m*-xylene, *o*-xylene, and *p*-xylene.
				Increase in spontaneous abortions in early pregnancy (human occupational exposure of 37 women exposed to xylenes and formalin in pathology and histology laboratories).[18]
			BO	Increased resorptions (rats, 775 ppm, mixed xylenes, inhalation).[18]
				Postimplantation loss (rats, 4500 mg *o*-xylene, inhalation).[18]
				Skeletal variations, delayed ossification, organ hemorrhages, decreased fetal weight (mice, rats, and rabbits, mixed xylenes, inhalation).[18]
				Increased incidences of cleft palate and decreased fetal body weight (mice, 2060 mg/kg/day mixed xylenes, oral).[18]
				Decreased fetal weight gain (rats, 3000 mg/m^3, *m*-xylene, inhalation).[18]
Xylenes	1330-20-7	2	F	Significant increase in delayed ossification, skeletal variation (rats, 2000 ppm *m*-xylene, inhalation).[18]
				Decreased fetal weight, skeletal retardation via gestational exposure (rats, 4500 mg *o*-xylene, inhalation).[18]
				Significant reduction in fetal body weight, gestational exposure (rats, 500 ppm *o*-xylene, inhalation).[18]
				Skeletal variations, incomplete ossification (rats, 2000 ppm *o*-xylene, inhalation).[18]
				significant increase in delayed ossification, skeletal variation (rats, 2000 ppm p-xylene, inhalation).[18]
			N	Decreased neuromuscular coordination (rats, 200 ppm mixed xylenes, inhalation).[18]
				Reductions in absolute brain weight and neurobehavioral effects (rats, 500 ppm mixed xylenes, inhalation).[18]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
				No adverse effects on the prostate, testes, ovaries, uterus, or mammary glands (mice, 2000 mg/kg mixed xylenes, oral; rats, 1000 mg/kg mixed xylenes, oral).[18]
				No adverse reproductive effects after chronic exposure (mice, 1000 mg/kg mixed xylenes, oral; rats, 5000 mg/kg mixed xylenes, oral).[18]
			FR	No adverse effects (rats, >500 ppm mixed xylenes, inhalation).[18]
				Reduced fertility (rats, 775 ppm mixed xylenes, inhalation).[18]
				No alterations in testes, glands, or male hormone levels (rats, 1000 ppm mixed xylenes, inhalation).[18]
				No effects on testicular weights (rats, 100 ppm *m*-xylene, inhalation).[18]
				31.5% mortality in dams (rats, 3100 mg/kg/day mixed xylenes, oral).[18]
			M	Maternal growth inhibition and maternal mortality (rats, 3000 mg/m^3 *m*-xylene, inhalation).[18]
				Decreased weight gain (rats, 3500−7000 mg/m^3 *p*-xylene, inhalation).[18]
Pentane	109-66-0	2	–	No studies on reproductive or developmental toxicity available.[17] According to the European Chemicals Agency, cyclohexane is oxidized to cyclohexanol, whose excretion and conjugation is identical to n-pentane so studies on cyclohexane can be used as reproductive and developmental toxicity indicators.[17]
Phenol	108-95-2	N	–	No adverse reproductive, developmental, or fertility effects seen in either human or animal studies of sufficient quality as determined by the Agency for Toxic Substances and Disease Registry, except at doses toxic to the mother.[18]
				No significant increase in the rate of miscarriage was found in a group of 576 women exposed to organic solvents relative to 576 unexposed pregnancies. Specific mention of phenol was reported in only five cases, all of which were normal deliveries (human occupational exposure in university laboratory, inhalation).
			F	Insufficient studies to establish teratogenicity.
				Reduced fetal body weight (rats, 7000−10000 ppm for 7 h per day, inhalation).[71]
1-Propanol	71-23-8	N	N	Biochemical changes in the brain (neonatal rats, oral).[71]
				Impaired male reproductive performance (rats, 15220 mg/m^3, inhalation).[71]
			FR	Decrease in absolute weight of testes (rats, 100 ppm for 6 h a day for 5 days a week for 4 weeks, inhalation).[72]
				No effects on the number of resorptions, still births, or preimplantation losses (mice, 0.5−10.0 mL/kg-day, oral).[73]
			BO	No effect on fetal survival (hamsters, 1550 mg/kg, oral; mice and rats, 1600 mg/kg, oral; rabbits, 1230 mg/kg, oral).[73]
				No significant change in number of abnormalities (hamsters, 1,550 mg/kg, oral; mice and rats, 1,600 mg/kg, oral; rabbits, 1,230 mg/kg, oral).[73]
				No effect on pup survival or body weight gain in pups (mice, 1−5%, oral).[73]
Propylene glycol	57-55-6	N	F	No significant differences in malformation or fetal body weight (mice, 0.5−10.0 mL/kg-day, oral).[73]
				Further animal studies and in vitro studies are available.[51,73]
			FR	No effects on number of litters, live pups, gestational period, and maternal weight at delivery (mice, 1−5% weight per volume, oral in drinking water).[73]
				No significant changes in male sex organs or sperm motility and count or female estrual cycle (mice, 1−5% weight per volume, oral in drinking water).[73]
			M	No effects on body weight, gravid uterine weight, and absolute liver and kidney weights (mice, 0.5−10.0 mL/kg-day, oral).[73]
			F	No human studies or quality animal studies (as determined by the Agency for Toxic Substances and Disease Registry) available on reproductive effects of pyridine.[18]
Pyridine	110-86-1	N		Very limited evidence of malformations and abnormal development at high doses (chicks, 10−20 mg pyridine/egg, injection).[18]
			FR	Limited evidence of adverse effects on male and female fertility that is dose dependent (mice, male effects at 250, 500, and 1000 ppm, no female effects, oral in drinking water; rats, male and female effects at 1000 ppm, no effect at 0, 250, or 500 ppm, oral in drinking water).[74]
				Increase incidence of spontaneous abortions (human occupational exposure, pregnant Finnish chemical workers employed in styrene production; human occupational exposure, polystyrene plastics processing).[18]
			BO	No increased risk of spontaneous abortions (human occupational exposure, processing polymerized plastics or heated plastics made of styrene).[18]
				No increase in stillbirths or fetal viability (human occupational exposure, case-control studies of pregnant plastics workers in Sweden and Norway).[18]
				Significant increase in stillbirths and resorbed fetuses (hamsters, 1000 ppm, inhalation).[18]
Styrene	100-42-5	2		No significant changes in fetal viability or resorption numbers (mice, 250 ppm, inhalation).[18]
				No fetal malformation or low birth weights (human occupational exposure, case-control studies of pregnant plastics workers in Sweden and Norway).[18]
			F	No significant increase in congenital malformations (human occupational exposure, pregnant reinforced plastics workers).[18]
				No significant developmental effects observed (rats, 300 and 600 ppm, inhalation; rats, 300 mg/kg, oral; rabbits, 600 ppm, inhalation).[18]
			N	Increase in neonatal deaths in offspring (rats, 300 ppm, inhalation).[18]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
				Delays in righting reflex and incisor eruption (rats, second generation offspring, 500 ppm, inhalation).[18]
				No menstrual disturbances or significant fertility effects (human occupational exposure, pregnant reinforced plastics workers, direct exposure of 52 ppm, indirect exposure of 13 ppm, inhalation).[18]
			FR	Significant decrease in sperm concentration, sperm count, normal sperm, and nonvital sperm in 23 male workers but no significant alterations in female workers' fertility (human occupation exposure, 6 months of working at a styrene manufacturing facility).[18]
				No significant changes in frequency of abnormal sperm heads (mice, 300 ppm, inhalation).[18]
				No alteration in reproductive performance, estrous cycle, spermatogenic parameters (rats, 500 ppm, inhalation).[18]
				Degeneration of seminiferous tubules and decreased spermatozoa and decrease in markers of testicular function (rats, 400 mg/kg, oral).[18]
				Increased in stillborn pups (mice, 1% of calories consumed, diet).[75]
			BO	Increase in resorptions and stillborn pups (mice, 1556 mg/kg-day, oral).[76]
				Increase in stillborn pups (rats, 1000 mg/kg-day, oral).[76]
			F	Depressed fetal weight skeletal variations (rats, 2000−5000 ppm, inhalation).[75]
			N	Decline in pup survival and male pup weight (rats, 1000 mg/kg-day, oral).[76]
tert-Butanol	75-65-0	N		No reduction in fertilizing capacity of spermatozoa (mice, 1000−4000 mg/L).[77]
			FR	Increased estrous cycle length (mice, 11620 mg/kg-day, oral).[76]
				Slight decrease in sperm motility (rats, 1000 mg/kg-day, oral).[76]
				No adverse effects on reproductive performance or sperm parameters (rats, 100−1600 ppm, inhalation).[76]
				Depressed maternal weight gain and food consumption (rats, 5000 ppm, inhalation).[75]
			M	Reduced weight gain and consumption (mice, 1% of calories, diet).[75]
				Severe signs of neurotoxicity and decreased consumption and body weight gain (rats, 1000 mg/kg-day, oral).[76]
			BO	No effect on implantations but reduced percentage of live fetuses (mice, 600−5000 ppm, inhalation).[17]
				No effect on the number of live fetuses per litter (rats, 600−5000 ppm, inhalation).[17]
				No effect on fetal weight (mice, 1800 and 5000 ppm, inhalation).[17]
				Low incidences of cleft palate, edema, ectopic ovaries, undescended testes, increased incidence of reduced ossifications (mice, 1800 ppm, inhalation).[17]
Tetrahydrofuran (THF)	109-99-9	2	F	Reduced body weight in first generation and second generation pups and delayed auditory canal opening and eye opening in second generation pups (rats, 1000−9000 ppm, oral).[17,40]
				Reduced fetal body weight at highest dose and no significant fetal malformations (rats, 600−5000 ppm, inhalation).[17]
				Reduced body weights and reduced ossification (rats, 5000 ppm, inhalation).[17]
			FR	No adverse effects in reproductive function (rats, 4000−12000 ppm, oral).[17]
			M	Reduced body weight and increased lethargy during gestation and lactation (rats, 1000−9000 ppm, oral).[17]
			BO	Increased risk of spontaneous abortion and preterm birth (human occupational exposure meta-analysis, mixed solvents including toluene, inhalation).[18,78]
				Increased risk of malformations (human occupational exposure meta-analysis, mixed solvents including toluene, inhalation).[18,78]
			F	Limited evidence of increased central nervous system anomalies and neural tube closure defects (human occupational exposure meta-analysis, small study of 14 women, mixed solvents including toluene, inhalation).[18]
Toluene	108-88-3	2		Malformations including microcephaly, central nervous system dysfunction, growth deficiency, craniofacial and limb abnormalities, and reversible renal tubular acidosis (human, toluene abuse study, inhalation).[18]
			N	Inconclusive evidence of neurobehavioral deficits at high doses—no effects at 200 or 400 ppm, adverse effects at 2000 ppm (mice, 200−2000 ppm for 60 min exposures 3 times a day during gestational days 12−17, inhalation), and no effects (rats, same exposure as mice).[18]
			FR	Inconclusive studies on male and female fertility effects, some showing effects, others no effects (rats, ≤ 2000 ppm, inhalation).[18]
			BO	Early embryonal deaths (chicken embryos, 1.0−4.0 μmol, injection).[17]
			F	Insufficient studies on the teratogenic effects of triethylamine.[41,79]
Triethylamine	121-44-8	N		Fetal malformations (chicken embryos, 0.5−4.0 μmol, injection).[17]
			FR	Insufficient studies on the reproductive effects of triethylamine.[41,79]
				No adverse reproductive effects observed (rats, 25−247 ppm, inhalation).[17]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 2. continued

Solvent	CAS number	GHS cat.[17,38]		Adverse effects
Trifluoroacetic acid (TFA)	76-05-1	N	BO	Disruption of ova development into normal blastocysts (rabbits, 10−20 mg/kg, oral).[79]
				Note: Studies have been carried with structurally similar salts (sodium trifluoroacetate, potassium trifluoroacetate (TFAK) and potassium trifluoromethanesulphinate (TFSK)) to prevent corrosive effects resulting from TFA.[17]
				Slightly low live birth index—the ratio of surviging number of offspirng after one day over total number of offspring—(rats, 8400 ppm of sodium trifluoroacetate, oral).
			F	No teratogenic effects (rats, 1400 ppm and 3400 ppm of sodium trifluoroacetate, oral).[17]
				No adverse effects on litters (rats, 100−1000 mg/kg-day TFAK and TFSK, oral).[17]
				No observed fetal abnormalities or variations and no effects on fetal body weight or ossification parameters (rats, 150 mg/kg-day TFA during organogenesis, oral).[17]
				Note: an extended, one-generation study on rats is ongoing, will be finalized October 2021.[17]
			N	Low body weight gain after birth (rats, 3400 ppm and 8400 ppm sodium trifluoroacetate, oral).[17]
			FR	No adverse effects on reproductive performance or reproductive organs (rats, 100−1000 mg/kg-day TFAK/TFSK, oral).[17]
			M	Low food consumption and body weight gain (rats, 8400 ppm gestation of sodium trifluoroacetate, oral).[17]
				No observed effects on consumption, body weight gain, placental weight, or uterine weight (rats, 150 mg/kg-day TFA, oral).[17]
Undecane	1120-21-4	N	BO	No effects on number of live pups delivered (rats, 300 and 1000 mg/kg, oral).[17]
				No effects on female sex cycle, conception, reproductive organ weights (rats, 300 and 1000 mg/kg, oral).[17]
			FR	No adverse reproductive effects (rats, 25−1000 mg/kg-day, oral).[17]
				No adverse reproductive effects (rats, 100−1000 mg/kg).[17]
			M	Body weight increase during lactation period (rats, 1000 mg/kg, oral).[17]

[a]Exposures described in adverse effects are maternal exposures unless otherwise noted. GHS classifications: 1A: Known human reproductive toxicant (based on human studies); 1B: Presumed human reproductive toxicant (based on mostly animal studies); 2: Suspected human reproductive toxicant (limited evidence in either human or animal studies); along with N: Not a GHS listed reproductive hazard (not enough information for classification). Adverse effects: BO: Birth outcome; F: Fetal effects; N: Neonatal and beyond effects; FR: Fertility effect; M: Maternal effects.

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Chem. Res. Toxicol. 2022, 35, 163−198

windows of vulnerability for pregnant researchers. The rapid changes occurring in both maternal and fetal organs over the course of a pregnancy from conception to birth alter the susceptibility to certain hazards and the severity of negative outcomes (Figure 2). For example, the placenta (technically a fetomaternal organ) alters the transport of some chemical hazards, such that for certain chemicals vulnerability would be greater in the time before placental formation but reduced afterward; a zygote or embryo is more vulnerable than a fetus to radiation hazards, as its lower bodyweight results in higher relative dose and to chemical hazards due to the critical development occurring during those stages; high radiation exposure during the first two weeks after conception is likely to induce a miscarriage, while during organogenesis, the critical period where human organs begin to form, malformations are the more likely outcome.[21]

2. LABORATORY CHEMICAL RISK

The concern with chemicals and chemical processes toward pregnancy outcomes arises from effects on both maternal and fetal health. Chemicals can impact maternal health via endocrine disruption, hypertension, or deficiencies, among others, and can impact fetal health—both directly and indirectly—via passage through or accumulation in the placenta causing oxidative stress, endocrine disruption, or alterations in gene expression and cell cycles, among many other possible effects.[26−29] In the following discussion, both oxidative stress and endocrine disruption are identified frequently as main underlying biochemical mechanisms of teratogenicity from exposure to certain chemicals, as they can interfere with critical developmental signaling and response processes. Oxidative stress occurs when xenobiotics interfere with redox-sensitive signaling pathways.[28] Prompted by reactive oxygen species (ROS) produced by natural electron leakage in mitochondria or various oxidases, redox switching of thiol redox couples tells cells in a developing fetus when to proliferate, when to differentiate, and when to begin apoptosis (programmed cell death). Some chemical hazards also have the potential to produce ROS, which when exposed to a developing fetus, can cause the misregulation of redox couples and incorrect signaling of cell activity. In addition, excess ROS-producing oxidative stress can lead to macromolecule and protein damage, lipid peroxidation, DNA oxidation, and necrosis (unprogrammed or accidental cell death).[28] Endocrine disruption occurs when xenobiotics mimic or interfere with hormone activity in the body.[30] Because endocrine-disrupting chemicals are a class of emerging chemicals of concern due to their effects on reproductive health of the mother, the father, and the fetus, they are discussed in detail as a chemical class of their own in Section 2.4.

Following an exposure in the lab, one of the most significant concerns for fetal health is whether or not the chemical crosses the placenta to the developing fetus (Figure 3a,b).[31,32] When fully formed, the placenta lessens fetal exposure through both retention and detoxification of xenobiotics. However, some xenobiotics have the ability to pass through the placental membranes, similar to nutrients, through three major mechanisms: diffusion, mediated active transport, or vesicular transport (Figure 3c).[31] Diffusion of chemicals from maternal blood into fetal blood can occur either by direct diffusion, where chemicals follow Fick's law of diffusion and are driven across the placenta and cell membranes through concentration gradients, or passive diffusion following paracellular passage, where chemicals pass through the space between placental cells, and then into fetal blood through passive diffusion.[31,32] Diffusion occurs mainly for small, relatively hydrophobic molecules, like respiratory gases and other hydrophobic chemicals.[31] Mediated active transport employs transporter proteins to facilitate the exchange of hydrophilic and charged molecules and has increased kinetics relative to diffusion.[31] For molecules too large to be transported by either diffusion or transporter proteins, vesicular transport through the membrane can occur by endocytosis, where a macromolecule in maternal blood is engulfed in the membrane, which pinches off to form a vesicle that passes through the membrane and subsequently releases the macromolecule into fetal blood.[31,33]

2.1. Organic Solvents. *2.1.1. Hazard.* Organic solvents are mostly carbon-based chemicals that are used ubiquitously in chemical laboratories for various applications including reactions, extractions, separations, cleaning, and more. Organic solvents often top the list of occupational hazards for pregnant researchers, as they tend to be volatile even at room temperature and many are known carcinogens, neurotoxins, and reproductive hazards.[35] "Solvents" as a general hazard are linked to negative reproductive effects like miscarriage, stillbirth, preterm birth, low birth weight, and birth defects in several population-based occupational studies.[7,35] As a result, known teratogenic effects in humans tend to rarely be specific to a single solvent, but rather to a mixture (also see Section 5). When working with several solvents simultaneously, it is hard to determine which specific solvent was associated with the observed effect in human studies.[36] Therefore, information on specific solvents relies heavily on animal studies as toxicity indicators.

Incorporating both human and animal studies, the Global Harmonization System (GHS) compiles information on reproductive toxicity into classifications based on available evidence, where GHS classification category 1A is a known human reproductive toxicant based on human studies, category 1B is a presumed human reproductive toxicant based on mostly animal studies, and category 2 is a suspected human reproductive toxicant based on limited evidence in either human or animal studies.[16] Table 2 compiles GHS classifications along with additional literature review on adverse reproductive effects for 50 common organic solvents. The 50 listed organic solvents were chosen as they represent the combined list of the top 25 most commonly used organic solvents based on a solvent-usage analysis by Jordan et al. of three journals: *Angewandte Chemie* (issue 1 in 2019), *Organic Process Research and Development* (all 2019 issues), and *Journal of Medicinal Chemistry* (issues 1 and 2 in 2019) along with a few other known problematic solvents[37] representing most solvents a pregnant researcher is likely to encounter. Additional information on other solvents can be accessed in searchable online databases, such as the European Chemicals Agency's chemical database or the Agency for Toxic Substances and Disease Registry's toxicological profiles, among others.[17,18,38−41] Notably, many compounds in Table 2 are listed as "not a GHS listed reproductive hazard" (Table 2). This does not mean that they are safe or not reproductive hazards, but rather, that insufficient information is available for classification, and more research is needed to make a determination.[17,38] Using the GHS classification and studies showing adverse effects, hazardous solvents can be identified and prioritized for elimination or substitution with potential alternatives in an effort to reduce risk. Recent green chemistry-

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 3. Common Heavy Metals Encountered in a Chemical Laboratory and Their Reproductive Effects Based on Information from Respective Toxicological Profiles from the Agency for Toxic Substances and Disease Registry[18] and Other Literature[a]

Metal		Adverse effects
Aluminum	F	Limited evidence of adverse effects dependent on form of aluminum. No observed maternal toxicity, embryotoxicity, or teratogenicity of aluminum hydroxide (rats and mice, oral) while other forms induced developmental alterations (rats and mice, aluminum chloride, aluminum nitrate, and aluminum lactate, oral).[27]
	N	Fetal skeletal variations, particularly with bioavailable forms of aluminum (rats and mice, aluminum nitrate and citrate, oral).[18]
		Adverse neurobehavioral and immune system effects (mice and rats, oral).[18,27]
	FR	No studies on reproductive effects in humans.
		No associations with adverse fertility effects (multiple studies, animals, oral).
		No histological changes in reproductive tissues (rats and guinea pigs, 6.1 mg Al/m^3 as aluminum chlorhydrate over 6 months, inhalation).[18]
	BO	Limited evidence as studies are not high quality.
		Increased incidence of spontaneous abortion (human occupational exposure, exposure scenario not clearly described, dust containing metallic antimony, antimony trioxide, and antimony pentasulfide, inhalation).[18]
Antimony	F	No associations with antimony levels in cord blood and adverse pregnancy outcomes (human epidemiology study).[18]
		No associations with neural tube defects or structural abnormalities (human epidemiology study, antimony in drinking water).[18]
	N	No overt developmental effects observed for offspring (human occupational exposure, exposure scenario not clearly described, dust containing metallic antimony, antimony trioxide, and antimony pentasulfide, inhalation).[18]
		Decreases in pup growth and alterations of the cardiovascular system (rats, 0.7 mg Sb/kg/day as antimony trichloride, antimony exposure.[18]
	FR	Increased incidence of menstrual disturbances (human occupational exposure, exposure scenario not clearly described, dust containing metallic antimony, antimony trioxide, and antimony pentasulfide, inhalation).[18]
		Adverse effects on ability to conceive in females (rats, inhalation).[18]
		No alterations in sperm parameters (rats, antimony trioxide or antimony potassium tartrate, oral).[18]
	BO	Significant increased incidence of miscarriages, stillbirths, preterm births (human population study, inorganic arsenic, oral exposure from drinking water;[18,94−96] human epidemiological studies, inorganic arsenic, inhalation).[18]
		Limited studies on increased risk of spontaneous abortion to occupational exposure of arsine gas (humans, inhalation).[40]
Arsenic	F	Fetal malformations including congenital heart and neural tube defects (humans, inorganic arsenic).[18,94,97]
		Fetal malformations including delayed ossification and irregular palatine rugae (mice, rats, and rabbits, methyl arsenates, oral).[18]
	N	Low birth weight (human population study, inorganic arsenic, oral exposure from drinking water; human epidemiological studies, inorganic arsenic, inhalation).[18]
	FR	No histological damage to reproductive tissues (animals, methyl arsenates, oral).[18]
	M	Increased risk of gestational diabetes (humans, oral drinking water).[94]
	BO	Limited evidence as studies are not high quality.
		Low birth weight (rodents, 180−200 mg barium/kg/day for 30 days of barium chloride, oral, not high quality study).[18]
Barium	F	Lower risk of malformations with higher barium levels, (human statistical study, barium in drinking water, conclusions are limited as the exposure scenario was not clearly described).[18]
		No adverse developmental effects (mice, up to highest dose of 200 mg barium/kg/day, oral).[18]
	FR	Adverse effects on male and female fertility with inhalation exposure (study of suspect quality), and following oral exposure studies are conflicting.[18]
		No alterations in sperm parameters (rats and mice, barium in drinking water for 60 days, oral).[18]
	BO	Increased fetal mortality and stillbirths (rats and mice, beryllium nitrate, beryllium oxide, and beryllium chloride, injection).[18]
Beryllium	N	No adverse developmental effects (dogs, beryllium sulfate in diet).[18]
		Behavioral abnormalities from beryllium crossing placenta and reaching fetus (mice, injection).[18]
	FR	No adverse fertility effects (dogs, beryllium sulfate in diet; rats, beryllium sulfate in drinking water; rats, beryllium oxide, injection).[18]
	BO	Embryonic death (rats, injection).[27]
	F	Malformations (mice, rats, and hamsters, injection).[27]
Cadmium	N	Low birth weight[98,99] and birth length[100,101] (humans).
		Retardation (mice and rats, injection).[27]
	FR	Endocrine disruptor and metalloestrogen causing female fertility effects (humans and rats, oral).[18,102]
		Inconclusive evidence of effect on male fertility with some studies showing effects and others not observing effects (humans, animals).[18]
	BO	Increased miscarriage (rats and mice, Cr^{6+}, oral).[18,103]
Chromium	F	Abnormal skeleton and reproductive system development (mice, Cr^{6+} as potassium dichromate and Cr^{3+} as chromium chloride, injection).[18,103]
		No developmental effects (rats, 1806 mg Cr^{3+}/kg/day as chromium oxide for 60 days before mating and throughout the gestational period, oral).[18]
	FR	Limited human evidence: inverse correlation between blood Cr levels and sperm count (human occupational exposure, exposed to Cr^{6+} for 1−15 years in an electroplating factory).[104]
		Inconclusive evidence in animal studies: adverse male fertility effects including reduced sperm mobility, sperm damage, and sperm death (mice, monkeys, rats, oral);[18,104] adverse female fertility effects (mice, Cr^{3+} and Cr^{6+}, oral); no adverse reproductive effects (mice, Cr^{3+} and Cr^{6+}, oral).[18]
	M	Complications during pregnancy and childbirth (toxicosis and postnatal hemorrhage) (humans occupational exposure, dichromate manufacturing facility, Cr^{6+}).[18]
Cobalt (stable)	BO	Maternal and fetal lethality at high doses, lower dose had significant increases in fetal mortality (rabbits, > 38 mg cobalt/kg/day cobalt; 7.6 mg cobalt/kg/day).[18]
	F	No developmental effects on human fetuses following treatment of pregnant women in third trimester (human, of 0.6 mg Co/kg/day of cobalt chloride for 90 days).[18]
		Effects on fetal skeletal formation (mice fetuses, 5 mM cobalt chloride, injection).[27]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 3. continued

Metal		Adverse effects
		No teratogenic effects (rats and mice, less than 38 mg cobalt/kg/day of cobalt sulfate; rats and mice, 24.8 mg cobalt/kg/day during gestation days 6−15 and 81.7 mg cobalt/kg/day during gestation days 8−12; mice, 5.4 or 21.8 mg cobalt/kg/day during gestation day 14 through postnatal lactation day 21).[18]
	N	Adverse effects on postnatal survival and development of pups, but was accompanied by overt maternal toxicity (rats, 5.4 or 21.8 mg cobalt/kg/day during gestation day 14 through postnatal lactation day 21, oral).[27]
	FR	Testicular degeneration and atrophy (rats and mice, 13 mg cobalt/kg/day cobalt chloride, chronic ingestion).[18]
	M	As an essential trace element, too low levels of Co in maternal blood were connected to pregnancy-induced hypertension and increased risk of preterm birth.[88]
	BO	Some studies have suggested a link between copper levels in human maternal blood and spontaneous abortion, but others have not found such evidence.[94]
	F	Malformations (rats and mice, copper sulfate and copper acetate, ingestion).[27]
		Significantly reduced sperm motility (human in vitro studies, metallic copper and copper ions).[18,27]
Copper		Sexual impotence (human occupational exposure, male workers, 111−434 mg/m^3 copper dust, study suspect in quality as there was no control group).[18]
	FR	Effects on sperm (rats, copper chloride, inhalation)[27] and negative effects on male sexual organs (rats, 0.95 or 1.4 mg Cu/kg/day for 26 days, injection).[18]
		No fertility effects (mink, 12 mg Cu/kg/day as copper sulfate in diet) or reproductive tissues (male and female mice and rats, 66 and 68 mg Cu/kg/day or 398 and 536 mg Cu/kg/day, respectively, oral).[18]
	M	Gestational diabetes and hypertension linked to higher levels of copper in maternal blood (human).[94]
	F	Reduced fetal weight, increased skeletal variations, and decreased number of viable implants at levels where maternal toxicity was observed (mice and hamsters, 12.5−100 mg/kg/d of gallium and gallium nitrate, injected).[27]
Gallium	FR	Limited evidence of male reproductive toxicity (rats and mice, gallium arsenide) but occupational exposures via inhalation of gallium arsenide are argued to not be primary contributors to male reproductive toxicity in humans.[105]
	BO	Recommended in report by the Health Council of The Netherlands to classify indium (III) salts as presumed human reproductive toxicants based on animal studies.[106]
		Increased resorptions and stillbirths (mice and rats, and rabbits, indium trichloride, oral).[106]
	F	External malformations and skeletal malformations (mice and rats, and rabbits, indium trichloride, oral; mice and rats, hamsters, indium trichloride, indium nitrate, injection).[106]
Indium		No adverse developmental effects (mice and rats, up to 100 mg/m^3 indium phosphide, inhalation).[106]
		Recommended in report by the Health Council of The Netherlands to classify indium phosphide and indium arsenide as suspected human reproductive toxicants based on animal studies.[106]
	FR	Decrease in weight of male reproductive organs and atrophy of male and female reproductive organs (rats and mice, indium phosphide, inhalation; hamsters, indium phosphide, intratracheal instillation; rats and hamsters, indium arsenide, intratracheal instillation).[106]
		No effects on ovulation, fertilization, or male tissues or reproductive parameters (mice, up to 250 mg/kg/day indium trichloride, oral).[106]
	BO	Some evidence of higher risk of spontaneous abortion,[27,102,107] miscarriage, stillbirth, preterm delivery[85,93,108] (human epidemiological studies, ≤10 μg/dL Pb in blood).[18]
	F	Malformations in animal models (birds, fish, rodents) but not in humans.[27,104]
		Low birth weight (human epidemiological studies, ≤10 μg/dL Pb in blood).[18,85,93,108]
	N	Neurodevelopmental impairment, increased risk of developmental delay, reduced IQ, and behavioral problems later in life (humans, 5−10 μg/dL Pb in blood[109]).[107,110,111]
Lead		In males, reduced sperm count and sperm damage, reproductive hormonal alterations, and reduced fertility (humans − numerous epidemiological studies,
	FR	≤10 μg/dL Pb in blood) and more severe effects including decreased fertility and histopathological damage to testes (a few human epidemiological studies, > 10 μg/dL Pb in blood).[18,93]
		In females, inconsistent results, some reproductive hormonal alterations, decreased fertility, and early onset of menopause, others no adverse effects (human epidemiological studies, ≤10 μg/dL Pb in blood).[18]
	F	No increases in birth defects observed (human occupational exposure, animals).[18]
		Adverse effects on neurological structures causing postnatal motor-, cognitive-, and behavioral impairments (human, airborne, drinking water, diet).[18,112]
	N	Unusually high incidence of infant mortality (one human study, manganese in drinking water, unclear whether deaths directly attributable to manganese exposure).[18]
Manganese		Infant height and weight negatively correlated with blood maternal manganese levels.[113]
		Loss of sex drive and low sperm count (human occupational exposure, inhalation).[18]
	FR	Sperm damage and adverse changes in male reproductive performance (animals, diet).[18]
		Little evidence of impairments in female fertility − decreased number of offspring (one rodent study, oral exposure before pregnancy).[18]
	BO	Increased rate of spontaneous abortions or resportions (human, mercuric chloride; hamsters, inorganic mercury; rats, metallic mercury vapors, inhalation; mice and rats, guinea pigs, monkeys, organic mercury, oral).[18]
	F	Malformations (rats, metallic mercury vapors, inhalation).[18]
Mercury	N	Neurological damage and adverse effects central nervous system (humans, methylmercury; mice and rats, hamsters, guinea pigs, organic mercury, oral).[18]
		No significant effect on male fertility (human occupational exposure, metallic mercury).[18]
	FR	Adverse effects on male fertility (animals, methylmercury, oral) and adverse effects on female fertility (rats and monkeys, methylmercury, oral).[18]
	BO	Increased rate of spontaneous abortions (16% versus 8.5% in compared group of pregnant construction workers; human occupational exposure at nickel refining plant, 0.08−0.196 mg Ni/m^3, primarily as nickel sulfate).[18]
Nickel	F	Increased rate of malformations (17% versus 6% in compared group of pregnant construction workers; human occupational exposure at nickel refining plant, 0.08−0.196 mg Ni/m^3, primarily as nickel sulfate).[18]
	N	Decreased birth weight (rats, 1.6 mg Ni/m^3 as nickel oxide 23.6 h/day on gestation days 1−21), although no effect at 0.8 mg Ni/m^3.[18]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 3. continued

Metal		Adverse effects
Palladium	FR	Limited evidence for male fertility effects including histological alterations, decreases in sperm concentration, motility, and abnormalities, and decreases in fertility (mice and rats, nickel subsulfide, nickel sulfate, nickel chloride, nickel nitrate, oral).[18]
	F	Not enough good evidence on fetal effects.[114]
		No apparent teratogenicity in one low quality study (chicken embryos, 20 mg/egg of palladium(II) chloride, injection).[114]
	FR	Limited evidence of adverse effects on testes and sperm in low quality studies (mice and rats, 0.02 mmol palladium(II) chloride, injected).[114]
Platinum	BO	Increased fetal mortality (rats, 13 mg/kg of cisplatin: $Pt(NH_3)_2Cl_2$, drug for cancer treatment).[115,116]
	F	No fetotoxic effects observed (rats, platinum metal, $PtCl_2$, $PtCl_4$ in diet).[115]
	N	Reduced birth weight (rats, 200 mg Pt/kg $Pt(SO_4)_2$ in diet; rats, Na_2PtCl_3).[115]
		Developmental toxicity (500 mg/kg/d of Pt-siloxane, Karstedt catalyst).[115]
	FR	Adverse effects on male fertility, known effect with cisplatin; limited data for other platinum compounds (rats, 9−18 mg/kg platinum chloride injection; rats, 1000 μM hexachloroplatinate or tetraammineplatinum(II) chloride, injection).[115,116]
		No adverse effects on male fertility (rats, up to 1000 μM hydrogen hexachloroplatinate; human sperm, metallic platinum).[115,116]
Selenium	BO	No change in pregnancy outcomes (ewes, 24 ppm selenium as sodium selenate in diet).[18]
	F	Excess selenium is a demonstrated teratogen in birds, effects include reduced hatchability, grossly deformed embryos lacking eyes and beaks, deformed wings and feet (chick, coot, duck, stilt, and grebe embryos, selenium as sodium selenite or sodium selenate in diet or injection).[18]
		No clear evidence linking selenium exposures to teratogenic effects in mammals.[18]
		May interfere with normal fetal development and result in malformations (sheep and cattle, high seleniferous diets).[18]
Silver	N	No studies on developmental effect from exposure via inhalation, oral, and dermal exist in humans.[18]
		Silver in drinking water linked to reduced volume of certain well defined brain regions (neonatal rats).[18]
		No evidence to support reproductive effects in humans from exposure via inhalation, oral, and dermal.[18]
	FR	Temporary histopathological damage to testicular tissue and effects on sperm morphology (male rats, silver nitrate, injection,).[18]
		Termination of pregnancy (monkeys, silver nitrate, injection).[18]
Strontium	BO	No teratogenic effects (rats, 82 mg strontium/kg/day as strontium nitrate, injection).[18]
		Increased incidences of adverse pregnancy outcomes (mortality from developmental anomalies, chromosomal anomalies, labor complications, and other unspecified perinatal conditions; humans, radioactive strontium-90).[18]
	F	Teratogenic effects (skeletal abnormalities) on the fetus from exposure to high doses during gestation (mice and rats, radioactive strontium-90, injection).[18]
	N	Impaired bone development (rickets) at high doses in young children (human, stable strontium, oral, no information available on gestational or neonatal exposure effects).[18]
		Limited evidence on the reproductive toxicity of stable strontium in humans; not directly harmful to human sperm (human sperm, strontium chloride, in vitro).[18]
	FR	Adverse reproductive effect from injected radioactive strontium.[18]
		Increase rate of fetal death and evidence of selective accumulation in the testis (male mice, radioactive strontium-90, injection).[18]
		Reduced number of oocytes, reduced reproductive capacity of offspring (female pregnant mice, radioactive strontium-90, injection).[18]
Tellurium	F	Recommended in report by the Health Council of The Netherlands to be classified as a presumed human reproductive toxicant based on animal studies.[117]
		Increased incidence of hydrocephalus and malformations (rats, rabbits, tellurium in diet).[117]
Thallium	F	Increased embryo lethality, dose-related growth retardation and growth inhibition (cultured rat embryos, 10−100 μg/mL thallium).[18]
		Reduced fetal weight, hydronephrosis, and absence of vertebral bodies (pregnant rats, injection of 2 mg thallium/kg/day as thallium sulfate).[18]
	FR	No human data but animal data suggests susceptibility of male reproductive system to thallium.[18]
		Decreased sperm motility, inhibition of β-glucuronidase activity and histopathological alterations of testes (rats, 0.74 mg thallium/kg/day as thallium sulfate administered in drinking water).[18]
	N	Crosses human placenta but data is limited regarding developmental effects. Existing data suggests it might be a potential developmental neurotoxicant.
		Causes alterations in the functional competence of the nervous system, impairment of learning observed after prenatal exposure (rats, 0.08 mg thallium/kg/day thallium sulfate).[18]
Tin	BO	Embryonic and fetal death at maternal toxic doses (rats, organotin compounds such as triphenyltin, dibutyltin, dioctyltin- *S,S'*-bis [isooctylmercaptoacetate].[104]
	F	Decreased fetal growth, reduced fetal ossification and other malformations at doses nontoxic to the mother and fetal growth suppression and cleft palate at maternal toxic doses (rats, organotin compounds such as triphenyltin and dibutyltin).[104]
	FR	Testicular degeneration (rats, tin(II) chloride 10 g/kg for 13 weeks in diet).[118]
		Abnormalities in the testes and ovaries (rats, triphenyltin hydroxide, oral).[118]
Titanium	Fr	No reproductive effects in humans reported from inhalation, oral or dermal exposure to titanium tetrachloride.[18]
		No histopathological alterations in the testis and epididymis (male rats, up to 40 mg/m3 titanium tetrachloride).[18]
	N	No studies on developmental effects in humans or animals from inhalation, oral or dermal exposure to titanium tetrachloride.[18]
Uranium	BO	Decrease in litter size, increased late resorptions and decreased live fetuses, increased neonatal death per litter, decreased day 21 viability index, reduced pup's weight (mice and rats, uranyl nitrate or uranyl acetate, oral).[18]
	N	Reduced body weight and length, increases incidences of malformation and developmental variation (mice, uranyl acetate dihydrate, oral).[27]
		Delayed hyperactivity, decreased spatial working memory (rats, enriched uranyl nitrate, oral).[18]
		Testicular degeneration linked to high oral doses (male rats, 331 mg U/kg/day as uranyl nitrate hexahydrate for 2 years in diet).[18]
	FR	3-fold increase in plasma testosterone, reduced pregnancy rate, disturbance in ovarian folliculogenesis, increased proportion of morphologically abnormal oocytes, increased oocyte dysmorphism and micronuclei in cumulus cells (mice and rats, 1.9−11.2 mg U/kg/day as uranyl nitrate or uranyl acetate, oral).[18]

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Chem. Res. Toxicol. 2022, 35, 163−198

Table 3. continued

Metal		Adverse effects
Vanadium	BO	Reduced pup weight and length, decreased viability, increased gross, skeletal and visceral anomalies, decreased pup body weight (mice and rats, sodium metavanadate, ammonium metavanadate, vanadyl sulfate).[18]
	F	Embryotoxicity and fetotoxicity (mice and rats, and hamsters, ingestion).[119]
	FR	Decreased fertility, sperm count, and motility (mice and rats, 31 mg V/kg/day vanadyl sulfate ammonium metavanadate, 25 mg V/kg/day sodium metavanadate).[18]
Zinc	BO	One adverse effect reported from oral consumption of 0.6 mg zinc/kg/day as zinc sulfate during third trimester (4 women study: 3 premature births, 1 still birth). Increased fetal resorption, reduced fetal weight, altered tissue concentration of fetal iron and copper, reduced growth in offspring, and still births (rats, dams, mice, zinc oxide, zinc carbonate, >200 mg zinc/kg/day in diet).[18]
	N	No studies on developmental effects in humans or animals after inhalation exposure to zinc exist.[18] No reproductive effects in humans after inhalation, oral (0.3 mg/kg/day).[18]
	FR	No adverse effect on mammary glands, ovaries, fallopian tubes, or uteri (mice and rats, and guinea pigs exposed to 119.3 or 121.7 mg zinc/m^3 as zinc chloride smoke for 20 weeks).[18] Altered sperm chromatin structure, decreased live pups per litter in all groups of treated rats, increased preimplantation loss, no reproduction in females (rats, 7−25 mg zinc/kg/day zinc chloride, 200 mg zinc/kg/day zinc sulfate, 250 mg zinc/kg/day zinc carbonate oral).[18]

[a]Adverse effects: BO: Birth outcome; F: Fetal effects; N: Neonatal and beyond effects; FR: Fertility effect; M: Maternal effects.

inspired solvent selection guides that incorporate hazard considerations have been put forward by the ACS Green Chemistry Institute pharmaceutical roundtable and the European public−private partnership, CHEM21, to identify safer alternatives that retain function.[42,43]

2.1.2. Exposure. Exposure time and concentration are significant in determining risk associated with organic solvent exposure.[53] For example, in a 1967 Russian epidemiologic study focusing on pregnant anesthesiologists exposed to ethyl ether and other agents, 18 out of 31 pregnancies ended in spontaneous abortion,[53] but those with higher exposure (>25 h per week) experienced abnormal pregnancies, while those with lower exposure (<15 h per week) experienced normal pregnancies (this study has limitations in that these women were exposed to different anesthetics and concentrations that may have also contributed to birth outcomes).[53] The Canadian Centre for Occupational Health and Safety, United States Occupational Safety and Health Administration (OSHA), and the United States National Institute for Occupational Safety and Health (NIOSH) have outlined a series of recommendations to minimize exposure to organic solvents,[80−82] although these are not specific to pregnant researchers. These recommendations include substitution with less hazardous solvents when possible, using the smallest amount of the solvent when substitution is not available and using solvents in appropriate fume hoods or, if not possible, in other well-ventilated areas to avoid inhalation.[80−82] If exposure cannot be avoided, a respirator with an appropriate cartridge for vapors of the organic solvent in question should be worn to protect against accidental inhalation. For some common organic solvents, OSHA has occupational permissible exposure limits for inhalation defined as average parts per million (ppm) concentration in air over an 8 h work day, also called 8 h time-weighted average (TWA).[82] These permissible exposure limits are for the general worker, but can be used as a first step for addressing laboratory inhalation exposure while keeping in mind that the fetus is often more vulnerable. To avoid dermal exposure, researchers should wear the appropriate type of solvent-resistant gloves and protective clothing. Though popular in laboratories, nitrile or latex gloves do not offer effective protection against all solvents.[81,83] Nitrile gloves are generally suitable for incidental contact with chemicals, but permeability varies by solvent (e.g., little protection from chlorinated solvents), while latex gloves provide little protection from organic solvents.[81,83] NIOSH and OHSA recommend checking the efficacy of the glove against the specific chemical in readily available glove chemical compatibility charts.[81,83] Depending on the solvent(s), a combination of several gloves may be necessary.[81,83]

2.1.3. Vulnerability. Clinical trials and retrospective observational studies conducted thus far on harmful impacts of organic solvent exposure during pregnancy have been limited to understanding overall effects when exposed to organic solvents throughout pregnancy. There are still many unknowns about the specific timeframes when solvents are most problematic to the health of the fetus.[78,84] The first trimester represents a critical period in fetal development, suggesting this may be a time to avoid dangerous organic solvents.[36] McMartin et al. observed a statistically significant relationship between exposure to organic solvents in the first trimester of pregnancy and fetal malformation, yet did not specify which solvents in particular are especially hazardous.[78] Thulstrup and Bonde found that there was an increased level of neural tube defects in newborns who were exposed to glycol esters during the first trimester of pregnancy.[85] However, it is important to be mindful of organic solvent exposure throughout the entire pregnancy, as research is still unclear about specific windows of vulnerability for most organic solvents.

2.2. Heavy Metals. *2.2.1. Hazard.* Metals, in various forms (e.g., elemental, salts, organometallics), are used in chemical laboratories, often as catalysts or reagents. Heavy metals can be defined as metals whose density is five times larger than that of water (i.e., specific gravity > 5), among others, but the designation "heavy metals" is often used as a catch-all term for a dense metal that is toxic at low concentrations, including lighter metals like aluminum (Al), some metalloids like arsenic (As) and nonmetals like selenium (Se), while excluding nontoxic high-density metals like gold (Au).[26,86] Some heavy metals such as cobalt (Co), copper (Cu), chromium (Cr), iron (Fe), manganese (Mn), nickel (Ni), selenium, and zinc (Zn) are essential minerals and trace elements that are found naturally in the human body, while others serve no known biological function. Exposure to essential metals in higher than recommended doses can have deleterious health effects including adverse reproductive outcomes,[26,27,87] while lower than recommended doses can increase risk of negative birth outcomes.[88] The placenta actively transports Cu, Zn, and Fe, such that increasing metal levels in maternal blood also result in higher levels in the fetal blood.[89]

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Chem. Res. Toxicol. 2022, 35, 163−198

Of the heavy metals, arsenic, cadmium (Cd), chromium, lead (Pb), and mercury (Hg) are the most studied due to exposures in residential and occupational settings.[35,85,90−93] Mechanisms of toxicity of heavy-metal exposure include oxidative cell stress (As, Cd, Cr, Pb), neurological damage (Hg, Pb), DNA damage (As, Cd, Cr), altered glucose metabolism (As), altered calcium metabolism (Cd, Pb), and general interference with essential elements inside the body (Cd, Hg).[26] Generally speaking, heavy-metal toxicity depends on aqueous solubility, oxidation state, and bioavailability, all of which depend on the form of metal.[87] For example, mercury in its organic form such as methylmercury (CH_3Hg^+; as opposed to elemental or salts of mercury) and arsenic as As(III) (as opposed to As(V)) are more soluble and more easily transportable in biological systems leading to greater toxicity concerns.[86] Furthermore, metal ions can interact with sulfhydryl groups found on proteins and enzymes, which can lead to the suppression of antioxidative processes and depletion of thiol-containing oxidants and enzymes, such as glutathione, and can result in the disruption of essential metabolic functions in the mother and/or the fetus.[33] As, Cd, Cr, Pb, and Hg are discussed in more detail below, and Table 3 contains an overview of known adverse reproductive effects for a variety of other heavy metals.

One of the most common global environmental metal contaminants, arsenic is commonly found in two different oxidation states as arsenate (As(V)) and arsenite (As(III)), the latter being the more toxic form and a known carcinogen.[120] Inorganic arsenic takes the forms of oxides, sulfides, and salts of copper, calcium, sodium, and iron, among others; organic arsenic takes the forms of methyl arsenates.[86] Arsenic has been shown to have endocrine disrupting properties in chicken embryos.[94] In humans, arsenic is known to cross the placenta and has been found in fetal tissue.[121] Exposure to arsenic at levels higher than 10 μg/L in drinking water has been linked to an increased risk of spontaneous abortion, while other adverse outcomes such as stillbirths, neonatal death, hypertension during pregnancy, and gestational diabetes have also been reported.[94,97] Impaired growth and development including fetal malformation and increased risk of fetal and infant mortality have also been reported due to arsenic exposure.[94−96] When arsenic reacts with an acid, it forms a toxic gas arsine (AsH_3), a colorless, nonirritating gas. After entering the blood stream via inhalation, it can damage red blood cells and is fatal to adults at high doses (30 min exposure 25−50 ppm).[40] Increased risk of spontaneous abortion in women exposed to arsine in the work place has been reported, though the studies have limitations due to sample size and lack of data about exposure to other chemicals.[40]

Cadmium can accumulate in the liver and kidneys, where it has been shown to be highly toxic.[86,122] The placenta appears to inhibit cadmium transport into fetal circulation since higher concentrations were reported in the placenta than in cord blood.[33] In fact, cadmium concentrations in the placenta have been shown to be 10 times higher than in maternal blood and 100 times higher than in cord blood, suggesting cadmium accumulation in the placenta.[92] Cadmium can lead to both reproductive and developmental effects on the fetus. Cadmium reproductive toxicity is linked to its endocrine disrupting activity and its effect on hormone production and binding capacity (especially progesterone and leptin).[26,94,111,123] Cadmium is a metalloestrogen, with one study showing that it acts as an estrogen receptor agonist in rats (also see Section 2.4 on endocrine disruptors).[102] While cadmium accumulation in fetal and embryonic cells is limited, it can interfere with DNA and protein synthesis.[27] Exposure to cadmium via injection has been linked to retardation, malformations, and even embryonic death in rats, malformations in hamsters, and retardation and malformations in mice.[27] Further, cadmium concentrations in the placenta, cord blood, and maternal blood have been reported to inversely affect birth weight[98,99] and length in humans.[100,101]

Chromium is found in the environment in all oxidation states between Cr^{2+} and Cr^{6+}, but the most common forms are trivalent chromium (Cr^{3+}) and hexavalent chromium (Cr^{6+}). Cr^{3+} is an essential nutritional supplement and plays an important role in glucose metabolism,[86] yet exposure to excess levels of Cr^{3+} can result in toxicity. Cr^{6+} is the more toxic form mainly due to its higher cell membrane permeability in comparison to Cr^{3+}.[86] Cr^{6+} is a strong oxidizing agent, which can form ROS inside cells, causing oxidative stress and DNA and protein damage.[86] In rats, ingestion of Cr^{6+} (250, 500, or 750 ppm as potassium dichromate, $K_2Cr_2O_7$) three months prior to gestation showed reduced implantation of fertilized eggs (increased resorptions), reduced number of fetuses, and pre- and postimplantation losses.[103] Fetal effects included subdermal hemorrhage on the thorax and abdomen and skeletal abnormalities due to reduced ossification.[103] In humans, exposure to chromium has been linked to congenital malformations, low birth weight, and DNA damage in some studies, while others have not been able to establish such links.[91,104,124]

Fetal lead exposure can be from exogenous sources (i.e., environmental exposure), but also from lead stored in maternal bones from prepregnancy exposures, which can be mobilized due to metabolic changes that take place to compensate for calcium deficiencies during pregnancy.[90,92,94,125] This latter endogenous exposure mechanism could account for 10−88% of lead found in the blood stream of pregnant women and is one of the reasons that lead exposure prior to pregnancy is a major concern (also see Section 5 on the exposome).[90] Once in the maternal blood stream, lead has been reported to be transported across the placenta via active transport[125] or via passive diffusion and can alter calcium-mediated cellular processes in the placenta.[27] Positive correlations between maternal blood concentrations and placenta concentrations have been reported.[92] However, other studies have reported lower lead concentrations in the placenta than in both maternal or cord blood indicating that lead may not accumulate in the placenta and passes through to the fetus.[92,126] There are also reports that lead can accumulate in fetal bones and livers at higher concentrations than in maternal tissue.[125] The United States' Centers for Disease Control and Prevention (CDC) cautions that prenatal exposure to lead in the range of 5−10 μg/dL[109] can result in neurodevelopmental impairment, increased risk of developmental delay, reduced IQ, and behavioral problems later in life.[107,110,111] Lead-induced malformations have also been reported in animal studies but not in humans.[27,104] While the evidence regarding birth outcomes is conflicting, there have been reports that high levels of lead exposure can lead to higher risk of spontaneous abortion,[27,102,107] miscarriage, stillbirth, preterm delivery,[26,113,126] low birth weight, reduced sperm count, and prolonged time to pregnancy due to endocrine disrupting properties in humans.[85,93,108] Studies have also reported

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Chem. Res. Toxicol. 2022, 35, 163−198

reduced maternal fecundity rate with increasing maternal blood lead level (>20 μg/dL).[93]

Mercury is the only metal that is liquid at room temperature. In its elemental form, its toxicity stems from the inhalation following evaporation, a vapor that is colorless and odorless; other forms include inorganic and organometallic compounds. Whether or not the placenta accumulates mercury to lessen fetal exposure is conflicting: Some studies describe accumulation of mercury in the placenta,[92] while others have reported 1.5−3× higher mercury levels in cord blood compared to maternal blood.[33,90] Mercury mainly targets the brain, kidneys, and liver. Because of its endocrine disrupting properties, mercury can affect reproductive processes and lead to impaired maternal fertility.[102] In humans, methyl mercury has been demonstrated to have inhibitory effects on DNA synthesis of fetal astrocytes.[27] Prenatal exposure to methyl mercury has been linked to cerebral palsy, mental retardation, and various other effects on brain function related to motor function, visual-spatial perception, language attention, and memory even at low level of exposure.[104] Some studies have also linked mercury to spontaneous abortion.[108]

2.2.2. Exposure. Modes of exposure to heavy metals are most commonly via ingestion of contaminated food or water, through use of household products or through inhalation or dermal contact either in residential or occupational settings.[33,102] For a pregnant researcher, oral exposure routes in the lab are the least likely unless there are circumstances where metals are retained on the skin and subsequently introduced accidentally into consumed food or water. Rather, dermal or inhalational exposure are likely the more common route of exposure in a lab setting. Penetration of metals through the skin from occupational exposure of metals such as chromium, copper, lead, and mercury has been reported.[87] For the inhalation route of exposure, the metal particles are deposited in the mucosa and transferred into the blood stream.[87] Factors such as particle size, shape, hygroscopicity, and surface charge determine where particle deposition in the respiratory tract occurs.[87] Most larger particles will be trapped in the nose, throat, and large bronchi or sediment in the alveoli, while submicron particles can diffuse through these structures.[87] Once deposited, the particles can be absorbed and thus enter the maternal blood stream. Subsequent heavy-metal exposure to the fetus can occur through the amniotic fluid, the placenta, or the umbilical cord.[89] Depending on the mode of exposure, varying effects can be observed. For example, if metals pass through the placenta, the fetus can be exposed to metals directly, resulting in direct effects, while accumulation of certain metals in the placenta can alter the normal functioning of the placenta itself and interfere with transport of essential elements, potentially leading to deleterious effects for the fetus.

As metals are a part of our daily lives and ubiquitous in many industrial processes, workplace guidelines for most heavy metals and allowable limits of exposure, especially for lead, mercury, arsenic, and cadmium, are available and can be easily accessed. The Agency for Toxic Substance and Disease Registry[18] provides information on exposure to various metals and other toxic agents and compiles information on various residential and occupational exposure limits for the general public. Minimal risk level limits for As are below acute oral doses of 0.05 mg/kg/day and chronic oral doses of 0.0003 mg/kg/day.[127] The OSHA 8 h TWA exposure limits for general workplace air quality are 0.01 mg/m^3 of organo-mercury and 0.1 mg/m^3 of Cd fumes and 0.2 mg/m^3 of Cd dust.[82] However, these are exposure limits for the general worker and are thus not specific for pregnant researchers. The only CDC recommendation specifically for pregnant researchers is for monitoring and follow-up testing of maternal blood lead levels when found to be higher than or equal to 5 μg/dL (50 μg/L) to allow for further intervention.[110] Dermal exposure can be reduced through the use of PPE, while protection against inhalation exposure can result from the proper use of a respirator considering the metal itself and the particle sizes (for nano sized metals, see Section 2.3).

2.2.3. Vulnerability. Though there is lack of trimester-based studies for many metals, there are studies reporting that the exposure to metal ions during the early gestational period increased the risk of fetus fatality and developmental anomalies.[27,102,107] In the first 14 weeks of pregnancy, exposure to heavy metals, such as lead and mercury, has been linked to higher rates of spontaneous abortion.[27,102,107] Lead transfer across the placenta has been shown in human fetuses as early as 14−16 weeks along with increasing concentrations in fetal tissue with advancing gestational age.[125] Further, elevated maternal blood Pb and Mn levels during the second trimester may be a significant risk factor for neural tube defects.[128] It has also been reported that the first, early second, and late third trimester could be heightened windows of vulnerability to vanadium toxicity and could result in fetal growth impairment.[129] In addition, exposure to heavy metals that have endocrine disrupting properties can affect the preconception phase. Snijder et al. have reported that occupational exposure to lead can have adverse effects on human reproduction leading to reduced sperm count in males, prolonged time to pregnancy, and reduced fecundity rate.[93]

2.3. Engineered Nanomaterials. *2.3.1. Hazard.* Engineered nanomaterials (ENMs) are a class of materials with at least one dimension <100 nm that are manufactured and designed (as opposed to naturally or incidentally occurring) for applications due to their high surface area and unique properties when compared to bulk materials of the same chemical composition.[130] ENMs are frequently synthesized and studied in their own right for the development of novel materials as well as for utilization in chemical, biological, and catalytic applications, among others. ENMs are a newer class of materials but are widespread in chemical laboratories, with research interest accelerating since the late 1990s and nanotechnology research initiatives established in almost all industrialized nations by the early 2000s.[130]

Since ENMs are an emerging class of materials, pregnancy-related toxicological information is nascent. Existing literature mainly covers animal studies and a few in vitro human placenta studies,[131,132] but collective evidence points to occupational exposure to ENMs being hazardous to fetal development and inducing placental stress in certain exposure scenarios.[132,133] Due to their nano size, ENMs can cross the placenta, enabling potentially deleterious direct contact with the fetus and internalization in placental and fetal cells. In contrast, this ability has also been identified as medically beneficial and has resulted in proposals for targeted transplacental drug delivery to treat pregnancy complications, prevent preterm birth, and in some cases increase fetal health.[32,134−136] The mechanism of transplacental passage depends on the size of ENM, with extremely small particles (typically <25 nm) crossing by paracellular passage and larger nanomaterials crossing by vesicular transport (Figure 3).[32] Many types of ENMs have the ability to create ROS which cause oxidative stress in cells,

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Chem. Res. Toxicol. 2022, 35, 163−198

leading to effects such as cell apoptosis and inflammation.[137] Some ENMs have also recently been identified as endocrine disruptors (also see Section 2.4).[109,138]

It is important to note that ENM toxicological effects (or lack thereof) vary widely based on many factors, complicating concise hazard information or single recommendations for safe work. ENMs encompass an extremely broad and diverse set of material compositions or types (e.g., carbon-based materials: carbon nanotubes, fullerenes, etc.; metal nanoparticles: gold, silver, copper, etc.; metal oxide nanoparticles: titanium dioxide, silica, ceria, iron oxides, etc.) that each have unique characteristics (e.g., size, shape, surface functionality, surface charge, crystallinity, solubility, aggregation behavior, etc.). Changing the material composition or a single characteristic of the same material can alter its properties substantially, including potential fetal toxicity.[139] For example, despite having the exact same chemical formula, titanium dioxide (TiO_2) nanoparticles have differing toxicities based on crystalline structure and the subsequent ability to produce more ROS and resulting oxidative stress.[140] Silica (SiO_2) nanoparticles showed different effects in mouse models based on size, dose, and surface functionality including fetal resorption (miscarriage) and restricted fetal growth but only at sizes <100 nm, at the highest doses, and without surface functionalization.[137] In several studies, incorporating surface coatings on ENMs was a way to reduce toxic effects; for silica nanoparticles, adding a surface coating of carboxyl or amine groups eliminated detrimental effects.[137] In addition, modifying the surface of single-walled carbon nanotubes with polyethylene glycol significantly reduced their cytotoxicity.[141]

Some general conclusions can be drawn, such as that size and surface coating are the most significant factors driving ENM induced embryonic toxicity and ability to cross the placenta and that ROS generating ability, aggregation behavior, and others factors also contribute, yet inconsistently across nanomaterial types. Typically, smaller particles were more toxic than larger particles, but for example, for silver nanoparticles, larger particles were more toxic than smaller ones at the same concentration.[133] Several reviews exist that cover the pregnancy-related health effects of many common ENM compositions and characteristics (reviews with many ENM types;[132,133,142] reviews with specific ENM composition information: Carbon-based ENMs,[131] platinum nanoparticles,[143] silver nanoparticles,[144] titanium dioxide nanoparticles[140]), yet the field is continuing to evolve quickly with the introduction of novel ENMs.

2.3.2. Exposure. Safety guidelines for nanomaterials are lagging behind more traditional chemicals for the general researcher, with a 2010 survey of university and public research laboratories worldwide showing 90% of respondents being unaware of local or national regulations for safe handling of nanomaterials and almost three-quarters reporting having little or no awareness of internal or lab scale rules.[145] Since then, the EU and the US have issued guidance on nano safety practices through ECHA[146] and NIOSH,[147] respectively, but recent surveys in other regions continue to show a lack of awareness of nanomaterial-specific safety and health policy plans.[148,149] Guidelines on ENM exposure specific to pregnant researchers are further lagging, although the routes of ENMs exposure are well-established including dermal and via inhalation.[145,150] There are some studies on dermal exposure, mainly focusing on metal oxide nanoparticles in cosmetics, with the general conclusion that nanoparticles do not pass through human skin immediately or with short duration exposures, but with repeated exposure can penetrate deeper into the skin and become internalized (e.g., 4.7−6.1% 4 mm diameter titania nanoparticle cosmetic applied directly to skin of pigs for 22 days resulted in skin penetration, 60 days of exposure resulted in internalization).[140,151,152] Therefore, avoidance of skin contact and appropriate PPE are recommended. ENMs in powder form can become aerosolized and may be suspended for extended periods of time, resulting in inhalational exposure.[150] As such, respirators are recommended whenever in an enclosed laboratory space where ENMs are being used. It is also preferable to work with powdered ENMs in special "nano" hoods that are designed to contain ENMs, thereby preventing their circulation in the laboratory atmosphere.[150] A potentially even more protective route is to suspend ENMs in water or solvents to prevent aerosolization altogether.

2.3.3. Vulnerability. There is evidence that both fetal exposure and resulting effects of ENMs are dependent on the gestational stage in pregnancy. Early evidence of this came from Yang et al. who investigated gold nanoparticles injected in pregnant mice at different gestational stages. The study found that at early stages of a pregnancy, gold nanoparticles accumulated at similar concentrations in both extraembryonic tissues and the fetus, while later in a pregnancy after formation of the placenta, gold nanoparticle concentration in the fetus dramatically decreased.[153] However, the reduced exposure did not equate with toxicity outcomes, as there were no observed adverse effects at any of the gold nanoparticle concentrations.[153] Gestation time influenced toxic effects of zinc oxide nanoparticles orally administered in mice: No fetal toxicity was found during early gestation, yet increased toxicity (i.e., decreased fetal viability) during late gestation after organogenesis.[132,154] Stapleton reviewed the effects of a range of ENMs focusing on exposures related to gestational time points, specifically at early gestation and midlate gestation (equivalent to before and after approximately 8 weeks of a human pregnancy).[155] While Stapleton concedes that the literature is limited for gestational exposure to ENMs, she identifies the following trends relying on animal studies, mainly mouse models.[155] During early gestation, inhalation exposure to some ENMs increased rates of unsuccessful implantation of embryos.[155] After implantation but still during early gestation, ENM exposure caused effects on maternal vascular development in relation to the placenta and severe effects on fetal development including increased fetal mortality. During midlate gestation, ENM exposure was dependent on the ability to translocate across the placenta, and in cases of ENM accumulation in placental or fetal tissues, increased placental ROS leading to oxidative stress, low birth weight, reduced fetal growth, and malformations were reported.[155]

2.4. Endocrine Disruptors and Other Chemicals of Concern. *2.4.1. Hazard.* Endocrine disruptors (EDCs) can be very broadly defined as exogenous substances or mixtures that interfere with normal, endogenous hormone action and consequently cause adverse health effects in the person exposed, or in their descendants.[156] EDCs can both be man-made or naturally occurring[157,158] and can be present in laboratories as chemicals being used in research or being studied. EDC exposure can impact the crucial functions that hormones play in regulating many physiological systems including in the brain, cardiovascular system, thyroid, pancreas, and importantly, the ovaries and uterus in females and testes and prostate in males.[156,157] As a result, a wide variety of

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Chem. Res. Toxicol. 2022, 35, 163−198

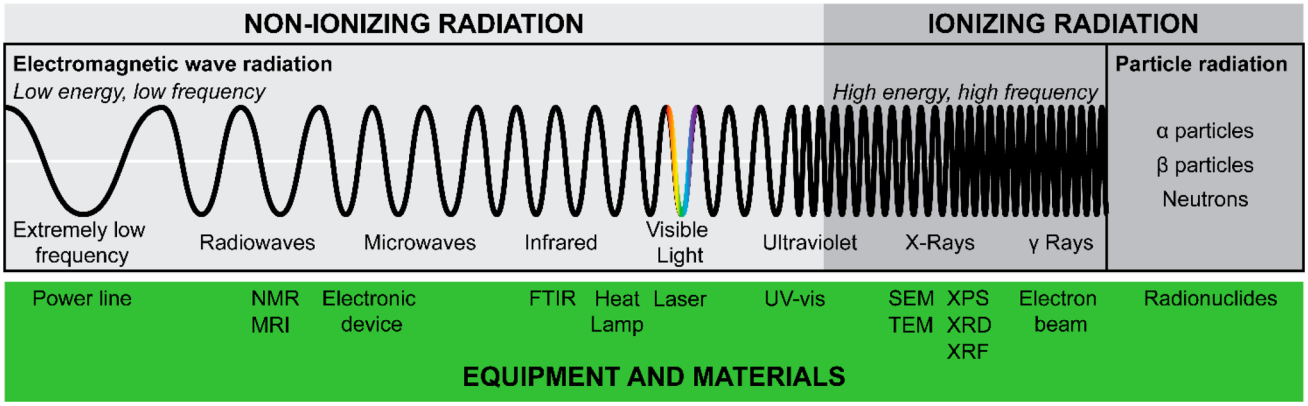

Figure 4. Types of radiation on the electromagnetic spectrum divided between nonionizing and ionizing radiation, alongside particle ionizing radiation. Noted are some common radiation sources, including ones found in chemical laboratories.[192]

negative health outcomes have been reported and are the subject of ongoing research including studies into the impacts of EDCs on reproductive health, thyroid-related disorders, hormone-related cancers, bone and metabolic disorders, and others summarized elsewhere.[156,157,159] Some of the better-studied EDCs include the bisphenol monomers such as bisphenol A (BPA),[159−162] phthalate plasticizers,[159,161,163,164] pesticides such as dichloro-diphenyl-trichloroethane (DDT) and atrazine,[159,165,166] polybrominated diphenyl ether (PBDE) flame retardants,[159,167] the environmentally persistent polychlorinated biphenyl (PCB) and dioxins,[159] the antibacterial triclosan,[168] paraben preservatives,[161] heavy metals such as lead, mercury, cadmium, and arsenic[94] (also see Section 2.2), and most recently perfluorooctanoic acid (PFOA) and other per- and polyfluorinated substances (PFAS).[159,169] Another recent debate revolves around potential endocrine effects of the herbicide glyphosate.[170] Beyond these notorious compounds, there are hundreds of compounds used in applications ranging from pharmaceuticals and personal care products to pesticides, industrial chemicals, metals, as well as naturally occurring compounds that have been identified as EDCs.[159,171−173] Given the sheer number of compounds that can be classified as EDCs, this review cannot provide a complete overview, but pregnant researchers should be particularly prudent when research is carried out on compounds with known bioactivity or endocrine disrupting ability, such as pharmaceuticals, pesticides, herbicides, fungicides, and others listed previously. This prudence should also extend to laboratory work involving precursors or degradation products of the above-mentioned classes of compounds, as these can be bioactive or endocrine disrupting themselves.

Of particular concern is prenatal exposure to EDCs in utero via transfer from the placenta,[174,175] which can impact the crucial development phases of the embryo, often permanently.[30] Animal studies (both mouse and rat) have shown that in utero exposure to EDCs can result in extreme, immediate effects such as pregnancy loss,[176] as well as effects that only become apparent during later stages in life from alterations in the hormonal balance such as early puberty, behavioral changes, altered breast development, and increased susceptibility for mammary cancer in female offspring; and reduced anogenital distance, delayed puberty, decreased fertility, and spermatogenesis in male offspring.[157] Adverse effects can even be passed on to following generations through epigenetic modifications.[157,165,177] In humans, in utero exposure to the EDC, diethylstilbestrol (DES), which was prescribed to pregnant women in the US until 1971 in the hopes of preventing miscarriages (it was shown that it in fact did not),[178] led to higher incidences of rare cervicogenital cancers, decreased fertility, and early menopause in daughters of women who used DES during pregnancy.[165,179]

2.4.2. Exposure. Chemical scientists and laboratory workers were among the 16% of jobs identified with probable exposure to endocrine disrupting chemicals based on a job-exposure matrix study of 348 occupations.[180] While exposure is probable, principal exposure in a chemical laboratory setting can be reasonably expected to stem mainly from inhalation, while dermal or oral exposure should play lesser roles when following typical safety protocols, as described earlier. Much of the known effects of EDCs are connected to oral exposure routes (e.g., orally administered DES, plasticizers in food or beverage containers, or EDC contaminated drinking water), and a few studies investigating occupational exposure show low risk of adverse birth outcomes.[181,182] For example, a meta-analysis of maternal occupational exposure to EDCs of approximately 134,000 mother-child pairs in Europe showed an association with increased risk of low birth weight when exposed to one or more EDCs, but did not find associations with length of gestation or preterm delivery.[180] The risk of low birth weight increased with exposure scenarios with more types of EDCs, up to four or more EDCs.[180] Another study of over 500 Danish women potentially exposed to EDCs showed no indications of reduced birth weight or increased risk of preterm birth compared to control groups.[182] Although these studies indicate low risk of adverse birth outcomes, due to the known adverse effects of EDCs on reproduction and development during exposure in utero and the lack of long-term results on offspring from occupational exposure, avoidance, substitution, or extreme caution is recommended when working with any known or suspected EDC in a chemical laboratory in general, and particularly during pregnancy.

2.4.3. Vulnerability. Specific vulnerability windows impacting the fetus' reproductive health are one of the main concerns about prenatal exposure to endocrine disruptors. Experiments with the known antiandrogens vinclozolin and some phthalates (e.g., benzylbutyl phthalate, dibutyl phthalate, di-2-ethly hexyl phthalate, and di-isononyl phthalate) have shown that the most sensitive period for fetal development is around gestational days 14−19 in rats, which corresponds to the "third trimester"

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Chem. Res. Toxicol. 2022, 35, 163−198

of the approximately 21-day long gestational period of rats.[24,25,164,166] Further, exposure to endocrine disruptors can result in permanent detrimental effects from the fetal stage through sexual maturation during puberty.[163,183,184] Such permanent changes can potentially be quantified following exposure, but may also become apparent only during adulthood.[160,185] In contrast, effects from exposure to endocrine disruptors such as BPA during adulthood may be reversible.[160] Nonetheless, endocrine disruptors can not only impact the reproductive health of the child pre- and postnatally, but they can also impact the preconception stage, including the ability of the couple to achieve a pregnancy, with the fertility of both partners potentially affected by endocrine disruptors.[186−191] For additional information, the Endocrine Disruption Exchange has an interactive timeline showing critical windows of developmental vulnerability as related to the development of the central nervous system, female and male reproductive systems, the endocrine system, the immune system, and other systems for the following EDCs: bisphenol A, dioxin, phthalates, chlorpyrifos, and PFAS (poly- and perfluoroalkyl substances).[24]

3. LABORATORY RADIATION RISKS

During certain tasks in chemical laboratories, pregnant researchers can be exposed to radiation. Radiation hazards include equipment and materials that produce either ionizing or nonionizing radiation (Figure 4). The following sections discuss these hazards as they relate to laboratory exposure and the potential impacts on pregnancy.

3.1. Ionizing Radiation Producing Equipment and Materials.

3.1.1. Hazard. Ionizing radiation hazards are present in chemical laboratories in the form of equipment and radioactive materials. Common laboratory equipment sources of ionizing radiation in the form of X-rays include X-ray diffraction (XRD), X-ray fluorescence (XRF), X-ray photo spectroscopy (XPS) and electron microscopes (SEM and TEM) in specific X-ray modes. In these instrument, X-rays are produced internally, and especially in older equipment, there is a potential for these to escape through weak points; newer equipment is typically adequately sealed with no X-ray leakage.[193] Electron beam equipment, such as probes and welders, can emit small levels of γ radiation. Furthermore, at larger specialized facilities, linear particle accelerators, ion implanters, cyclotrons, synchrotrons, and other electron ion accelerators can also emit ionizing radiation.

In contrast to equipment that only produces radiation when energized (i.e., turned on), some materials can continually emit ionizing radiation through radioactive decay.[192,194] These materials are referred to as radionuclides, such as tritium (^{3}H, often in the form of tritiated water, β emitter), carbon-14 (^{14}C, β emitter), phosphourus-32 (^{32}P, β emitter), sulfur-35 (^{35}S, β emitter), nickel (^{59}Ni, β and γ emitter; ^{63}Ni, β emitter), iodine-125 (^{125}I, γ emitter), and americium-241 (^{241}Am, α emitter). There are several other radionuclides, but use of these materials often requires special permission from governments and they are not likely to be in the average chemical laboratory.[194] Radioactive compounds are used as tracers or stains in experiments and in trace amounts in equipment, like household smoke detectors containing ^{241}Am or gas chromatography detectors utilizing ^{3}H or ^{63}Ni.[194]

Effects of ionizing radiation on humans are relatively well-documented and thoroughly researched with data available from radioactive incidents (e.g., Hiroshima, Nagasaki, Chernobyl, etc.) and medical occupational exposure (e.g., interventional radiology and cardiology), including effects related to pregnant women and embryos/fetuses.[8,21,195,196] Some ionizing radiation exposure can result in harmful effects, most commonly embryo/fetal lethality, organ malformations, intrauterine growth retardation, mental impairments, genetic anomalies, and childhood cancers.[21,195] These effects occur because ionizing radiation can cause direct cell and DNA damage. These severe effects are highly dependent on exposure dose and gestational age as explained below. It is also important to note that while for radiation-producing equipment, doses to the fetus are related directly to the exposure level for the mother, exposure to radionuclides is more complex, as these can accumulate in the fetus (including postnatally during breastfeeding), which can lead to higher direct exposure of the fetus than the mother.[21,196]

3.1.2. Exposure. Exposure to radiation is dose-dependent and expressed in either exposure dose (common unit: Roentgen, R; SI unit: C/kg), absorbed dose (common unit: Rad, rad; SI unit: Gray, Gy), or equivalent dose (common unit: Rem, rem; SI unit: Sievert, Sv). Absorbed dose (Gy) describes the amount of radiation energy absorbed by the mass of tissue regardless of the type of radiation, while equivalent dose (Sv) incorporates weighting factors for each type of radiation (e.g., α-particles $\gg$ β particles $>$ γ rays) and type of tissue to calculate a full body dose.[21] Exposure recommendations are typically given as an equivalent dose in mSv, while studies typically report absorbed dose in Gy as a threshold dose—the dose level below which no adverse effects were observed.

The United States Nuclear Regulatory Commission recommends that the pregnant worker should not be exposed to more than 5 mSv per pregnancy with a limit of 0.5 mSv/month.[8] The International Commission of Radiological Protection recommends that exposure not exceed 1 mSv during pregnancy, which is consistent with the US National Council on Radiation Protection.[196] Studies show no evidence that embryonal/fetal doses of 0.1 Gy or less (equivalent to 100 mSv for γ radiation and biological tissue) are associated with negative effects,[8,21] but there are still many uncertainties about the ramifications of prenatal radiation exposure, which explains the radiation exposure recommendations of <5 mSv total per pregnancy.[21,197]

Exposure to a pregnant researcher inside a chemical lab is likely no larger than what can reasonably be expected for an occupational or diagnostic radiation professional. For reference, a single, direct chest X-ray is 0.1 mSv;[198] occupational exposure for interventional radiologists with 1 mm-thick lead protection was measured at 0.03 mSv/month;[8] and the self-reported normal background radiation of an XRD lab was 0.0002−0.0005 mSv/hr, resulting in a maximum exposure of 0.12 mSv/month (assuming maximum accumulative exposure for 8 h days for 30 days).[199] A recent review recommended a three-pronged approach to safe work "using dosimetry data as a guide, tailoring use of personal and ancillary lead shielding, and active [laboratory] practices that can minimize occupational dose".[8] Shielding is often sufficient to keep fetal exposure below dangerous levels and can be achieved through individual or combinations of shielding materials and forms.[8] In addition to wearing appropriate shielding, OSHA guidelines more broadly recommend minimizing the time spent in areas

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Chem. Res. Toxicol. 2022, 35, 163−198

with elevated radiation levels and maximizing the distance from radiation sources.[8,194]

3.1.3. Vulnerability. Windows of vulnerability for high doses of ionizing radiation are better understood and more clearly defined due to (the unfortunate) availability of data from radioactive incidents. A pregnancy is particularly vulnerable to radiation in the first two weeks after conception when the principal effect of radiation exposure is failure of embryo implantation and early abortion at a threshold dose of 0.1 Gy.[21,195,200] During the organogenesis period, radiation exposure can cause intrauterine mortality at a threshold dose of 0.1−0.5 Gy and organ malformations at a threshold dose of 0.05−0.5 Gy.[195] Important brain development occurs between 10 and 27 weeks, when increased risk of intrauterine mortality, severe mental retardation, seizures, and reduced IQ can occur at a threshold dose of at least 0.1 Gy.[195] The developing brain gradually becomes less radiosensitive around 18 weeks when the threshold dose increases to 0.3 Gy.[195] After 27 weeks, the central nervous system becomes relatively more radioresistant with no cases of severe mental retardation observed in children from Nagasaki and Hiroshima exposed only after 27 weeks.[21,195,200] For miscarriage/intrauterine mortality, the threshold dose needed for increased risk rises as pregnancy progresses, where a dose of 0.1 Gy is associated with higher risk in implantation at weeks 2−4, 0.1−0.5 Gy from weeks 5−27, and >1.0 Gy past 27 weeks to full term.[195] Generally speaking, there is little evidence of increased risk from ionizing radiation to pregnant researchers at below these threshold doses.[8,21,195]

3.2. Non-Ionizing Radiation Producing Equipment.

3.2.1. Hazard. In chemical laboratories, some distinct nonionizing radiation producing equipment include heat lamps, lasers, and spectroscopy equipment like ultraviolet−visible, Fourier-transform infrared, and nuclear magnetic resonance (NMR). The CDC states that most common nonionizing radiation from radio frequencies (RF) to ultraviolet (see Figure 4) is not considered uniquely hazardous to pregnancies.[7,192] The only unique concern is the ability of nonionizing radiation to generate heat. Depending on wavelength, direct exposure to nonionizing radiation can potentially result in an increase of maternal internal body temperature, which can be hazardous to a developing fetus (also see Section 4.2 on heat stress).[7,192]

Types of nonionizing radiation that pregnant researchers may be in contact with are ultrahigh magnetic fields (UH-MF) coupled with the RF range (see Figure 4) in NMR or MRI and extremely low frequency magnetic fields (ELF-MF) from electronic equipment. UH-MFs are utilized in magnetic resonance equipment like NMR in chemical laboratories and MRI in medical facilities. Although the majority of literature focuses on the safety of a direct MRI scan and MRI occupational exposure for pregnant women rather than NMR, the core technology is the same so comparisons can be drawn.[201,202] Both NMRs and MRIs utilize more than one magnetic field to acquire data or images, including a high strength, static field, and a relatively low strength RF field. NMR and MRI machines are often referenced by their static magnetic field strength which, along with the molecule being measured, determine the operating frequency of the RF field used during measurement. Static magnetic field strengths range from 2.3−23.5 T for NMRs and 1.5−10.5 T for MRIs.[202] RF fields are present during the spectroscopy/imaging process and range in frequencies of 10−1000s of MHz and field strengths on the order of 1−100 μT. While the RF field is lower than the static field, its operating frequency causes the potential for maternal heating. However, both animal and human studies on MRIs do not indicate an increased risk of adverse outcomes. In a study on mice exposed to 75 min daily of 1.5 or 7 T UH-MFs (a direct MRI scan) during pregnancy, no effects were observed on pregnancy rate, duration, litter size, malformations, sex distribution, or postpartum death of offspring.[203] A 2020 literature review of pregnant women concluded that "MRI does not pose any known risks to the fetus though longitudinal data are lacking".[204]

Regarding ELF-MFs, there is much debate since a 1979 study showed higher incidences of childhood leukemia in children living in close proximity to power transmission lines, with the hypothesis that it was linked to ELF-MF exposure.[205,206] To date, no mechanism has been conclusively identified for if or how ELF-MF nonionizing radiation causes cancer, although it is labeled "possibly carcinogenic" by the WHO's International Agency for Research on Cancer.[207] Studies into ELF-MF nonionizing radiation and pregnancy have shown varying results, with some indicating increased risk of miscarriage and decreased fetal growth.[205,207,208] As exposure to ELF-MF occurs in, but is not unique to, chemical laboratories, pregnant researchers should be aware of it and are referred to other references and reviews.[205,207,208]

3.2.2. Exposure. Exposure guidelines do not exist for NMR occupational exposure, but the American College of Radiation guidance document on magnetic resonance safety states that it is permissible for pregnant healthcare practitioners to work in and around MRIs as long as they do not remain within the MRI scanner bore during the data acquisition period.[209] This recommendation stems from the fact that the strength of the static magnetic field fades as one moves farther away from the magnetic source. The strength of magnetic fields is inversely related to distance from the magnetic center cubed ($1/r^3$). The American College of Radiation also states that research has shown no harmful effects to the fetus from exposure to a magnetic field lower than 3 T.[209] In addition, newer NMR equipment (since 1995) usually integrates active shielding that limits stray magnetic fields, so the rated maximum field of the instrument is likely not the field being experienced in the environment next to the magnet.[202]

3.2.3. Vulnerability. To our knowledge, there are no trimester-based studies that directly address magnetic field exposure from NMR. For MRI, nearly all of the reviewed studies considered data from second and third trimesters, most likely due to policies and recommendations against MRI scans in the first trimester.[204] For example, in the UK, it is currently not recommended to collect MRI scans in the first trimester,[201] although it remains unclear what studies are being used to support this recommendation. Interestingly, a small study of women who received an MRI in the first trimester before their pregnancy was known showed no adverse outcomes.[204]

4. LABORATORY STRESSORS

Perhaps surprisingly, even the ambient state of some laboratory environments may pose risks that adversely affect pregnancies. Less obvious than chemical or radiation hazards, latent stressors such as excessive noise or heat, strenuous physical work, abnormal experimental schedules, or conventional psychosocial stress, should be mitigated for pregnant researchers.

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Chem. Res. Toxicol. 2022, 35, 163−198

4.1. Noise Stress. Sonicators, centrifuges, pumps, vacuum systems, and venting liquid nitrogen tanks are often staples in chemical laboratories and may generate dangerous levels of noise. A "loud" environment is defined at 90 dB by OSHA and 85 dB by the American Conference of Governmental Industrial Hygienists as the threshold noise level for an 8 h TWA shift to prevent work-related hearing loss.[210] Since wearing personal protective equipment such as hearing protection does not protect the fetus, noise reduction should be sought via substitution with quieter equipment, installing noise shielding, or other mitigation measures. The fetus's developing hearing system is more sensitive than a fully developed one, and the fetus has mostly developed ears by week 20 and starts to respond to external sounds by week 24. While the womb does provide some noise shielding mostly to high and medium frequency sounds, it does not provide sufficient protection against excessive noise and leaves the fetus particularly vulnerable to low frequency sounds. Selender et al. performed a population based cohort study that included over 1.4 million births from mothers with occupational exposure to noise at levels <75 dB, between 75 and 85 dB, and >85 dB.[210] This study showed an association between maternal exposures to >85 dB and hearing dysfunction in children, with a stronger association with more days worked in the loud environment, and no association for noise levels below 75 dB. Some limited evidence shows a slightly increased risk of low birth weight or preterm birth at levels exceeding 85 dB, but studies are inconclusive with others showing no increased risk.[35,211,212] More research is needed to identify an appropriate noise level limit in the 75−85 dB range and to determine whether exposure during early pregnancy is as detrimental as during later stages in the pregnancy after fetal hearing has developed, but reducing the noise level to under 75 dB is advisable based on the available data.

4.2. Heat Stress. Prolonged exposure to hot environments—whether around ovens, reactors, nonionizing radiation producing equipment, or nonair-conditioned laboratories during the summer—can induce heat stress in pregnant researchers who are more vulnerable to heat as their bodies need to work harder to cool down compared to nonpregnant people.[7] According to the CDC, heat stress, defined as any work situation that causes body temperature to exceed 39 °C or 102.2 °F, can lead to heat stroke, exhaustion, or dehydration in mothers and correspondingly has been linked to reproductive issues and birth defects in the fetus.[7] Beyond the recommendation not to exceed a maternal 2 °C body temperature increase, fetal health effects of heat exposure are less defined. A recent review on extreme ambient heat and pregnancy outcomes in studies that combine a population-based approach with geographic temperature data showed that maternal exposures to extreme heat can be associated with preterm birth, low birth weight, stillbirth, and congenital heart defects.[213] Windows of higher vulnerability for preterm birth, low birth weight, and stillbirth, appeared during exposures in the third trimester, while for congenital heart defects, exposures in weeks 2−8 were most important as the fetal heart is developing in this time frame.[213] The review did not identify temperature-related risks on the individual level as many of the evaluated studies defined "extreme heat" as relative to the preceding week's temperature conditions or relative to geographic location.[213] Therefore, no single recommendation for "acceptable" heat can be made.

4.3. Psychosocial and Physical Stress. Stress related to work, a type of psychosocial stress, can disrupt the endocrine system due to a heightened stress response (often leading to irregular menstrual cycles in women).[35,214] Recent evidence suggests psychosocial stress during pregnancy may induce stress responses and affect androgenic activity in the developing fetus, potentially leading to negative birth outcomes including preterm delivery, low birth weight, and spontaneous abortion.[35,214−217] Reviews on psychosocial stress and pregnancy outcomes examined both acute psychosocial stress (e.g., stress related to an earthquake disaster or the 9/11 terrorist attack) and chronic psychosocial stress (e.g., anxiety, household stress, job stress, among others).[35,214−217] While for acute stress, some evidence of association with negative birth outcomes was shown, particularly when experienced in the first trimester, literature on chronic psychosocial stress contained conflicting outcomes. There was evidence of a modest association of increased risk for preterm birth and low birth weight, but little evidence of increased risk of spontaneous abortion with some studies showing no associations with chronic stress.[35,214−217] Chronic stress experienced in the third trimester (week 30) had a higher risk of preterm birth than in the second trimester (week 16).[217] A caveat to these studies is that work-related stress is just one of many stressors, making it difficult to attribute increased risk directly to specific work-related stress.

Physical stress such as heavy physical work, heavy lifting, prolonged standing, and long or irregular work hours contains some risk of undesired birth outcomes and has been reviewed in detail.[35,108,216] Specifically, heavy physical work, frequent heavy lifting, and prolonged standing have been implicated in low birth weight, preterm birth, and spontaneous abortion, but with only modest risk.[108,216] Frequent heavy lifting has been linked to spontaneous abortion and is of particular concern during the third trimester, with increased risk for early uterine contractions and preterm birth.[35] Working in a lab can lead to abnormal hours, and working nights or irregular hours can affect the pregnant researcher's circadian rhythm and contribute to spontaneous abortions.[35] The study cohorts where these effects were observed were in fields where pregnant women were consistently subjected to heavy physical stress (e.g., nurses lifting and moving patients daily), which may or may not be applicable to pregnant researchers in laboratories.

5. MOVING BEYOND CONVENTIONAL RISK ASSESSMENT

Exposure to endogenous chemicals during pregnancy and lactation is ubiquitous.[218] Research based on representative sampling of the population at large[219] has documented that virtually every pregnant woman in the USA has at least 43 different environmental chemicals in her body and that persistent organic pollutants are found in pregnant and lactating women across the globe.[20,220] A report by the US National Cancer Institute found that "to a disturbing extent babies are born 'pre-polluted'".[221] However, conventional risk management for pregnant researchers typically entails reviewing anticipated laboratory situations and generating a "safe work" plan. This approach has significant limitations as exposures in lab are compounded by additional exposures over one's entire lifetime, and fetal windows of vulnerability have yet to be identified for many hazards. As evidenced by this literature review and mentioned elsewhere,[222,223] the vast

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Chem. Res. Toxicol. 2022, 35, 163−198

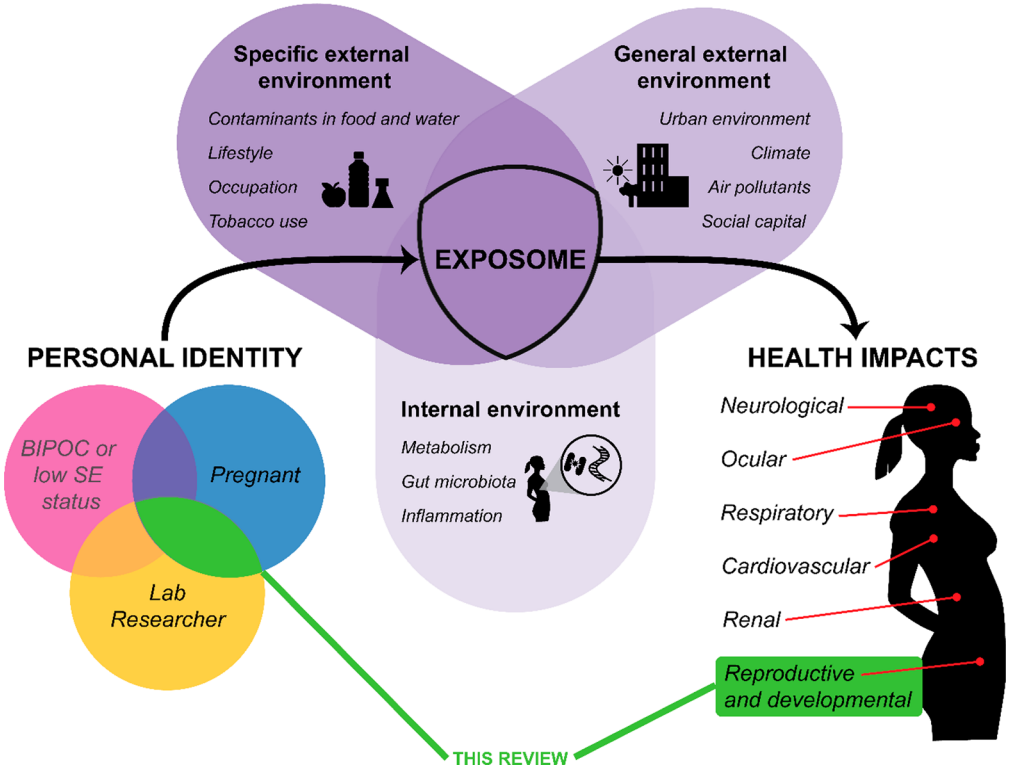

Figure 5. Personal identity (including, for example, identifying as black, indigenous, or a person of color (BIPOC) or low socioeconomic status (SE)) can impact each person's unique exposome, which arises from their specific external, general external, and internal environments, which can lead to health impacts over an entire lifetime of exposures. This review focuses specifically on pregnant lab researchers and potential reproductive and developmental health impacts resulting from exposure via their occupation (e.g., a specific external environment).[222,228]

majority of available reproductive and developmental toxicity studies examine single exposures—in both time and hazard—and the resulting adverse effects are often observed in animal models that do not necessarily translate into similar effects in humans.[15] In reality, multiple exposures can occur simultaneously, often with unknown combinatorial effects including antagonistic, additive, or synergistic interactions ("cocktail effects").[224] For EDCs and neonatal effects specifically, a recent study reported that being exposed to an EDC mixture of four or more versus a single EDC increased risk of low birth weight.[181] Yet, for many emerging contaminants of concern, it is difficult to draw firm inferences at present about issues such as critical dose and the period(s) of greatest vulnerability.[225] These examples emphasize the increasing importance to expand the current state of science as it relates to the toxicological implications of chemical mixtures and windows of vulnerability, especially those related to prenatal exposures.

Efforts to describe one's complete risk profile have been enhanced with the introduction of the concept of the "exposome," defined as each person's unique entire lifetime environmental exposures from conception onward (a complementary concept to each person's unique genome).[226] The exposome addresses the need to move beyond single exposure-health effect relationships by incorporating the complexity of exposures through time and to mixtures of multiple substances and environmental factors (Figure 5). Current exposome studies, such as the ongoing Human Early-Life Exposome prospective study,[222,223] incorporate many hazards simultaneously, amassing external environmental factors like atmospheric pollutants, noise, temperature, and community features like green spaces with internal environmental exposures like water pollutants, chemicals, and lifestyle choices. These exposures are studied starting from the prenatal period into childhood along with varying health outcomes.[222,223,227,228] While these studies help to understand the effects of prenatal exposure on the pregnant researchers' developing fetus, a better understanding of pregnant person's exposome would be important to better assess and predict potential effects on the pregnancy and child health.

Exposome studies have begun to make linkages between specific environmental factors (e.g., workplace), general environmental factors (e.g., social capital, urban environment), and internal factors (e.g., transcriptomics, metabolomics) to inform individual health risk assessments and impact outcomes (Figure 5).[229,230] It is important to note that this review only covers a small portion of specific environmental factors within one's exposome and that other specific and general environmental as well as individual factors will also impact the course of a pregnancy (Figure 5). Additionally, the exposome paradigm elevates the importance of intersectionality when considering compounding exposures and increased baseline vulnerabilities related to race, gender, sexual orientation, and socioeconomic status.[227,231] For example, it is well established that industrial facilities, sources of external environmental exposure, are historically more likely to be located in minority and/or low income communities,[232−234] thereby leading to adverse health and well-being outcomes (Figure 5). These profound issues of environmental justice have complex interactions with questions related to who is over- and underrepresented as laboratory researchers due to access, opportunities, and wellness warranting further exploration and are worthy of their own study and critical review.

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Chem. Res. Toxicol. 2022, 35, 163−198

Finally, for many hazards, there is often insufficient information regarding reproductive toxicity and resulting pregnancy outcomes in general, and specific windows of vulnerability in particular. Addressing these presents a significant opportunity for advancing computational toxicology, high-throughput screening, and predictive modeling. As of 2011, the US Environmental Protection Agency's ToxCast project began profiling the in vitro bioactivity of chemicals to assess pathway-level and cell-based signatures that correlate with observed in vivo toxicity to reveal meaningful mechanistic relationships and providing models to identify chemicals with potential developmental toxicity.[235] While advances in these areas will inform further studies to elucidate risk concerns, the anatomic, physiologic, and pharmacologic complexities of the systems at play as well as the varied potential compensation mechanisms are not yet able to be sufficiently well-modeled to enable a conclusion of safety.[236] However, there remains significant promise of the potential of these advanced techniques to identify stressors of concern from a developmental toxicity perspective as well as generate far more granular data in terms of timing of exposures and windows of vulnerability. Of course, the highest value of this new knowledge will be to inform the design of safer chemicals with reduced or eliminated inherent hazards, thereby reducing or eliminating potential developmental risks to pregnant individuals and their offspring, including lab researchers.[11,237] Through the development and implementation of green chemistry, benefits accrue not only to pregnant researchers and their future offspring but also to the broad research community and society at large, the ultimate end users of the discoveries, as well as historically disadvantaged communities in the vicinities of chemical production facilities. Further, safe chemicals and chemical processes will lead to overall gains in public and ecosystem health in support of a more sustainable future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemrestox.1c00380.

A table containing a curated selection of references including excellent reviews and resources for hazards of concern for pregnant researchers in chemical laboratories (PDF)

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