**Name of Journal:** *World Journal of Stem Cells*

**Manuscript NO:** 46729

**Manuscript Type:** REVIEW

**Effects of environmental stressors on stem cells**

Worley JR *et al*. Environmental stressors and SCs

Jessica R Worley, Graham C Parker

**Jessica R Worley, Graham C Parker**, Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI 48202, United States

**ORCID number:** Jessica R Worley (0000-0002-6460-5987); Graham C Parker (0000-0001-7963-5735).

**Author contributions:** Parker GC and Worley JR contributed equally to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

**Supported by** the Center for Urban Responses to Environmental Stressors Grant from the National Institute of Environmental Health Sciences, No. P30 ES020957.

**Conflict-of-interest statement:** The authors declare no potential conflicts of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding author:** **Graham C Parker, BSc, PhD, Research Assistant Professor,** Department of Pediatrics, Wayne State University School of Medicine, Integrative Biosciences Building, 6135 Woodward Avenue, Detroit, MI 48202, United States. gparker@med.wayne.edu

**Telephone:** +1-313-5772707

**Fax:** +1-313-9728024

**Received:** March 2, 2019

**Peer-review started:** March 4, 2019

**First decision:** June 5,2019

**Revised:** July 12, 2019

**Accepted:** September 4, 2019

**Article in press:**

**Published online:**

**Abstract**

Environmental toxicants are ubiquitous, and many are known to cause harmful health effects. However, much of what we know or think we know concerning the targets and long-term effects of exposure to environmental stressors is sadly lacking. Toxicant exposure may have health effects that are currently mischaracterized or at least mechanistically incompletely understood. While much of the recent excitement about stem cells (SCs) focuses on their potential as therapeutic agents, they also offer a valuable resource to give us insight into the mechanisms and risks of toxicant effects. Not only as a response to the increasing ethical pressure to reduce animal testing, SC studies allow us valuable insight into the true effects of human exposure to environmental stressors under controlled conditions. We present a review of the history of publications on the effects of environmental stressors on SCs, followed by a consolidation of the literature over the past five years on a subset of key environmental stressors of importance to human health and their effects on both embryonic and tissue SCs. The review will make constructive suggestions as to areas of toxicant research where further studies are needed, as well as making indications of the potential utility for advancing knowledge and directing research on environmental toxicology.

**Key words:** Environmental substances; Toxic; Stem cells; Endocrine disruptors; Alcohols; Tobacco smoking; Metals; Heavy; Particulate matter; Volatile organic compounds; Ozone

© **The Author(s) 2019**. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Environmental toxicants can cause health effects. While most research and discussion of stem cells focuses on their potential as therapeutic agents, they also offer a valuable resource to give us insight into the mechanism and incidence of the effects of environmental toxicants. We present a review of the history of relevant publications, followed by a consolidation of the literature over the past five years on a subset of key environmental stressors of importance to human health. Constructive suggestions as to the areas of toxicant research where further studies are needed, and indications of the potential for advancing knowledge are made.

Worley JR, Parker GC. Effects of environmental stressors on stem cells. *World J Stem Cells* 2019; In press

**INTRODUCTION**

Humans are chronically exposed to environmental stressors, pollutants of natural or anthropic origin which can have the effect of altering normal biological processes. While we have long known that many environmental toxicants, such as Lead (Pb) and Mercury (Hg), have deleterious effects on human health, the mechanisms by which these occur are not fully understood[[1](#_ENREF_1)]. Further compelling the imperative to more thoroughly understand the biological mechanisms behind these environmental toxicants are recent findings that their effects are transgenerational, echoing resulting outcomes far beyond initial exposure[[2](#_ENREF_2)].

While much attention has been given to the therapeutic potential of stem cells (SCs)[[3](#_ENREF_3)], their ability to serve as barometers of the toxic effects of environmental stressors should not be understated[[4](#_ENREF_4)]. As the body’s raw materials, SCs and their responses to environmental insult serve as windows into the pathways of disease. In this review, we highlight this much overlooked intersection of the study of environmental stressors and their impact on SC health.

Both tissue and embryonic SCs (ESCs) are seen as resources for the repair and regeneration of human tissues[[5](#_ENREF_5)]. SCs are also thought to maintain these tissues for the lifespan of the individual through their key characteristics of self-renewal and differentiation into specialized cells. Healthy SC function includes balanced cell proliferation and sufficient capacity for appropriate differentiation. We focus on the effects of environmental stressors that impact these operations. We also examine cell viability to analyze toxicity and provide a fuller picture of a toxicant’s effect, by correlating cell number to cell behavior[[6](#_ENREF_6),[7](#_ENREF_7)].

We began by a careful search to numerate the publications examining the effects of environmental stressors on SC populations. The goal was to achieve a better understanding of the history of this research as well as understand how research on individual stressors has changed over that time. We then made a more focused search of PubMed for research in the last five years on known environmental toxicants and SCs.

A list of known environmental agents whose exposure is known to cause adverse health effects in humans was drawn from the National Institute of Environmental Health Sciences (NIEHS)[[8](#_ENREF_8)]. These environmental toxicants were cross-referenced with the United States Comprehensive Environmental Response, Compensation, and Liability Act Priority List of Hazardous Substances as outlined in the Agency for Toxic Substances and Disease Registry (ATSDR) 2017 substance priority list (SPL)- “the government’s list, in order of priority, of substances most commonly found at waste facility sites on the National Priorities List (NPL) that are determined to pose the most significant potential threat to human health due to their known or suspected toxicity and potential for human exposure”[[9](#_ENREF_9)]. Each substance on the list is given an impact score, derived from an algorithm, with higher scores denoting those substances that most frequently appear at NPL sites, their known toxicity, and potential for human exposure, and then ranked by order of highest to lowest impact. Findings were summarized into a list of 20 environmental toxicants, including four heavy metals, ten endocrine disruptors, and six other important substances.

Table 1 outlines these toxicants with the corresponding highest rank of each substance within its class in the 2017 ATSDR SPL. For example, Arsenic (As) is listed at a rank of #1, with a score of 1674, derived from an algorithm that factors its ubiquity at NPL sites, its high toxicity, and the large risk for human exposure. The heavy metals, Pb, As, and Hg claim the top three spots on the list while the Volatile Organic Compound (VOC), Vinyl Chloride, ranks #4 on the list. Several other VOCs, like Benzene and Trichloroethylene, are also included on the ATSDR SPL. However, we record the highest ranked substance (Vinyl Chloride) for each toxicant class in our table, along with their score.

**LITERATURE SEARCH**

A keyword search was then performed in PubMed including the name of the environmental toxicant and SCs, *e.g.,* “Cadmium and stem cells” or “Particulate matter and stem cells” that were published from 2014 - June 2019. For each query, counts were recorded of total number of articles, review articles, and original research articles, and recorded in Table 2. On the topic of radiation and SCs, only those articles which treated radiation as an environmental exposure, as opposed to a tool for directed differentiation, were included. Our findings are classified again into three different classes: heavy metals, endocrine disruptors, and other environmental toxicants known to have deleterious human health effects. A separate PubMed search was conducted for each of the 20 toxicants, including the substance name and SC, *e.g.*, “Phthalates and stem cells” without a time limitation. Key class members’ data are presented in Figure 1-3: separated as Figure 1. Heavy metals, Figure 2. Endocrine disruptors, and Figure 3. Other environmental toxicants.The figures illustrate PubMed publication counts for the substances plotted against time in years, from 1953, the earliest publication on SCs and one of the listed environmental toxicants, up until June 2019. The findings of our PubMed literature review from 2014- June 2019 are presented in Table 3-5, with toxicants organized again into three classes: Table 3; Heavy metals, Table 4; Endocrine disruptors, and Table 5. Other environmental toxicants. The results are presented by mechanism of action as pertaining to SC viability, differentiation, and proliferation. Each table is then followed by a more focused discussion of key references, the mechanism of action and their associated health outcomes.

**HEAVY METALS**

Heavy metals are ubiquitous in the human environment and their toxicity is associated with varied adverse health effects depending on the dose, route and duration of exposure. Of the top ten chemicals on the 2017 ATSDR SPL, four of these are heavy metals: As, Pb, Hg, and Cadmium (Cd)[[9](#_ENREF_9)].

Pb is a persistent environmental toxin that for more than a hundred years has been known to have harmful human health effects[[10](#_ENREF_10)]. Pb exposure in neural SCs (NSCs) was shown to slightly reduce cell proliferation[[11](#_ENREF_11)]. Pb exposure was also shown to induce changes in microgliosis and astrogliogenesis in the hippocampus of mice, interfering with normal neurogenesis[[12](#_ENREF_12)]. Bone marrow-derived mesenchymal SCs (BM-MSCs) in rats showed an inversely proportional relationship between osteocalcin expression, a gene key to osteogenesis and Pb intake[[13](#_ENREF_13)]. In a striking finding, DNA methylation changes in the fetal germ cells of pregnant mothers exposed to Pb were carried over to her grandchildren[[2](#_ENREF_2)].

As is a known human carcinogen and is rated as the number one substance of concern on the ATSDR’s 2017 SPL. It is a naturally occurring element that when combined with oxygen, chlorine, or sulfur can form inorganic as compounds. In embryonic mouse SCs, As inhibited differentiation into neurons and myotubes[[14](#_ENREF_14)]. Differentiation, specifically osteogenesis and chondrogenesis, was also decreased in murine adipose-derived MSCs (AD-MSCs) after exposure to inorganic As[[15](#_ENREF_15)]. In human induced pluripotent SCs, As exposure was shown to create a dose-dependent sequence of morphology changes, a decrease in viability, and induced genotoxicity[[16](#_ENREF_16)].

Hg is a heavy metal with known associations to neuroinflammation, immunotoxicity, behavioral disorders, and adverse kidney effects. Mice exposed to 50 μmol of HgCl2 experienced an increase in hematopoietic SC (HSC) proliferation, while those exposed to the higher dose of 100 μmol HgCl2 saw HSC suppression[[17](#_ENREF_17)]. Hg exposure suppressed embryonic murine NSCs neural differentiation at as low as 10 pmol concentration within 7 d and inhibited neural and glial differentiation by day 14. Moreover, Hg concentrations over 100 pmol suppressed NSC differentiation to motor or dopaminergic neurons[[18](#_ENREF_18)].

Cd is a naturally occurring toxic metal in the earth’s crust, typing extracted as a byproduct in the mining for other metals. It is commonly found in batteries, dyes, and some metal and plastic products. Low levels of Cd exposure decreased cell number and proliferation and induced apoptosis in adult human neural progenitor cells (NPCs)[[19](#_ENREF_19)]. HSCs exposed to CD over three months experienced an increase in long-term HSCs, a loss in long-term potential, and promoted myelopoiesis[[20](#_ENREF_20)].

Endocrine disruptors are chemicals or chemical mixtures that interfere with the proper function of hormones and can be naturally occurring, such as phytoestrogens, or synthesized as in plastics, plasticizer, pesticides, fungicides, and pharmaceuticals[[21](#_ENREF_21)]. In this review, we include organophosphorus compounds (OPs), polycyclic aromatic hydrocarbons (PAHs), bisphenol A (BPA), dioxins, phthalates, organotins, dichlorodiphenyltrichloroethane (DDT), diethylstilbestrol (DES), polychlorinated biphenyls (PCBs), and per- and polyfluoroalkyl substances (PFAS).

PAHs are highly persistent organic compounds primarily released through both naturally occurring and man-made combustion, such as smoking or burning of fuel[[22](#_ENREF_22)]. NSCs exposed to the PAH, benzo(a)pyrene (BaP), showed impairment in the transition from cell replication to neurodifferentiation, resulting in higher cell number, but reduced cell size and damaged neuronal features such as neurite formation and the development of dopamine and acetylcholine phenotypes[[23](#_ENREF_23)]. BaP also decreased self-renewal and osteoblast differentiation of human BM-MSCs[[24](#_ENREF_24)]. Mice exposed orally to BaP experienced spermatogonial SC (SSC) mutations with different phases of spermatogenesis exhibiting varying sensitivities to BaP[[25](#_ENREF_25)]. In AD-MSCs, BaP did not inhibit cell proliferation, but did significantly inhibit adipocyte differentiation potential[[26](#_ENREF_26)]. In human skeletal muscle-derived progenitor cells, low doses of BaP repressed myogenic differentiation without causing cell toxicity. When BaP exposure was withdrawn, the inhibitory effects on myogenesis were reversed[[27](#_ENREF_27)].

OPs include the highly toxic nerve agent, sarin, as well as commonly used pesticides because of their inhibition of acetylcholinesterase. NPCs exposed to the OP pesticides paraoxon and mipafox during retinoic acid-induced differentiation showed reduced cell viability at high concentrations. Only paraoxon was shown to alter the process of neurodifferentiation[[28](#_ENREF_28)].

The concern over the harmful health effects of BPA, a xenoestrogen used in the making of plastics, has been widely popularized in the media, leading the United States Food and Drug Administration to abandon its endorsement of its use in baby bottles[[29](#_ENREF_29)] BPA is also commonly found in sports equipment, food and beverage packaging, and thermal paper products. In BM- MSCs, BPA exposure led to a dose-responsive increase in cytotoxicity, along with increased lipid peroxidation. BPA altered the response of proteins key in the regulation of fate and differentiation of human mammary epithelial SCs[[30](#_ENREF_30)]. Low level BPA exposure altered differentiation of prostate epithelial SCs toward basal progenitors, reducing commitment to luminal progenitor cells, while increasing SC size and proliferation[[31](#_ENREF_31)].

Dioxins include chlorinated dibenzo-p-dioxins, chlorinated dibenzofurans and certain PCBs. Dioxins are highly toxic, persistent compounds that are typically released into the environment through industrial incineration and bleaching processes. Exposure to the dioxin 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), the most toxic dioxin, was shown to impair human B cell development by reducing lineage commitment in HSCS[[32](#_ENREF_32)]. TCDD was also shown to suppress hematopoietic progenitor cells and accelerate their differentiation to mature lineages[[32](#_ENREF_32)]. HSCs in the fetal livers of offspring of TCDD-exposed mice experienced increased HSC proliferation, but B and T lymphocyte differentiation was significantly decreased[[33](#_ENREF_33)]. TCDD exposure activated the aryl hydrocarbon receptor (AHR) in the fetus of pregnant mice, leading to impairment of the long-term self-renewal of HSCs[[34](#_ENREF_34)]. In BM-MSCs, AHR activation by TCDD decreased osteoblast differentiation, possibly by suppressing the expression of the protein, β-catenin[[35](#_ENREF_35)].

Phthalates are a group of chemicals primarily used to soften plastics and due to the prevalence of plastic products, exposure is widespread in the United States population. HSCs were exposed to four phthalates: dibutyl phthalate (DBP), benzylbutyl phthalate, diethyl phthalate (DEP), and diethylhexyl phthalate (DEHP), and all four compounds were shown to reduce cell viability[[6](#_ENREF_6)]. NSCs exposed to DEHP also showed reduced cell viability, along with increased apoptosis due to reactive oxidative stress[[36](#_ENREF_36)]. DEP and DBP also reduced cell viability in the ESCs of mice[[37](#_ENREF_37)].

Organotins include tributyltin (TBT) and triphenyltin, substances with strong antibacterial and fungicidal properties that were historically used as marine anti-fouling additives in paint. Baker *et al*[[38](#_ENREF_38)] showed that in BM-MSCs, TBT activated adipogenesis and reduced osteogenesis. This finding was also supported in primary BM-MSCs for both TBT and tryphenyltin[[39](#_ENREF_39)].

DDT, an organochlorine developed as an insecticide was banned in the United States in 1972 after public outcry over its health effects, most notably outlined in Rachel Carson’s famous work, *Silent Spring*[[40](#_ENREF_40)]. However, DDT is a persistent organic pollutant, maintaining long-term exposure to organisms in the soil. When BM-MSCs were exposed to DDT, they exhibited altered morphology and inhibited self-renewal capacity, along with dose-dependent increased proliferation and differentiation[[41](#_ENREF_41)].

DES is a synthetic estrogen that was prescribed by the United States physicians from 1938-1971, to prevent miscarriages and avoid other pregnancy problems, but was later found to cause a rare vaginal cancer to girls exposed in utero[[42](#_ENREF_42)]. DES exposure in SSCs increased DNA damage, induced apoptosis, and superoxide anions[[43](#_ENREF_43)].

PCBs are intentionally produced, stable aromatic chlorinated hydrocarbons commonly used as coolants in electrical equipment, as lubricants and plasticizers. Some PCBs are “dioxin-like” (DL-PCBs) and others are non-dioxin-like (NDL-PCBs), with the distinction owing to the site of chlorine substitution on the phenyl rings. DL- PCBs have congeners with no or only one chlorine substitution in the ortho position have toxic effects similar to dioxins and bind strongly to the AHR[[44](#_ENREF_44)]. The remaining NDL-PCB congeners, who have been linked through epidemiological studies with prostate cancer, have unique toxic effects and thus we examine them a separate category of toxicant[[45](#_ENREF_45)]. Human exposure occurs from improper storage and spillage of PCBs, where they bind strongly to soil and enter food sources. Liver progenitor cells exposed to the NDL-PCB, PCB153, experienced significant changes in the S1P/ceramide (Cer) ratio, known to be crucial in determining cell fate[[46](#_ENREF_46)].

PFAS are a group of manmade chemicals that are used in including stain- and water-repellent fabrics, nonstick coatings, polishes, paints, and fire-fighting foams. They are very persistent compounds and thus can be found in water, soil, and organisms. Epidemiological studies have linked PFAS exposure to increased cholesterol levels[[47](#_ENREF_47)]. SSCs exposed to PFAS did not experience a decrease in germ cell viability, an increase in reactive oxygen species (ROS), or reduced cell viability[[48](#_ENREF_48)].

**RADIATION**

Ionizing radiation, a common treatment for cancer, is known to induce ROS by altering cellular metabolism and is known to reduce numbers of bone marrow HSCs and alter differentiation[[49](#_ENREF_49),[50](#_ENREF_50)]. However, the lower-intensity radiofrequency radiation, now rampant in society due to increased cell-phone and electronic use was shown to have only a mild effect on DNA damage and no effect on HSC apoptosis, ROS, cell cycle or DNA repair[[51](#_ENREF_51)].

**ALCOHOL**

Alcohol, known by its chemical name, ethanol, is mainly consumed via liquor, wine, and beer in order to create a psychoactive effect. Acetaldehyde, an endogenous and alcohol-derived metabolite, was shown to create DNA double-stranded breaks in HSCs. These breaks altered homeostasis by stimulating recombination repair, causing chromosome rearrangements, and inducing myelopoiesis[[52](#_ENREF_52)]. Chronic alcohol consumption in mice was also shown to disrupt homeostasis in intestinal SCs (ISCs), in part, through the β-catenin pathway, suppressing proliferation of ISCs[[53](#_ENREF_53)]. In human ESCs, alcohol was shown to stimulate differentiation by increasing the influx and metabolism of retinol[[54](#_ENREF_54)].

**TOBACCO SMOKING**

Cigarette smoking and the associated nicotine exposure is a notorious carcinogen and is the leading cause of preventable death in the United States[[55](#_ENREF_55)]. While tobacco smoke is also considered a VOC and its smoke is known to contain PAHs, we treat it separately here due to its known severe health implications. Smoking is known to induce oxidative damage in SCs[[56](#_ENREF_56)]. AD-MSCs exposed to cigarette smoke extract had significant impairment to cell viability, proliferation, and experienced genetic level variations in differentiation[[57](#_ENREF_57)]. Moreover, electronic cigarette extract exposure showed detrimental effects on BM-MSC morphology and proliferation[[58](#_ENREF_58)]. ESCs exposed to cigarette smoke condensate produced altered gene expressions, reduced viability, and induced apoptosis[[59](#_ENREF_59)].

It is important to note that PAHs are known to be present in cigarette smoking. However, for the purpose of this review, we have examined the effects of cigarette smoking and PAH exposure on SCs separately.

**PARTICULATE MATTER**

Particulate matter (PM) are fine particles of air pollution whose potential to harm health is directly related to their size and capacity for inhalation[[60](#_ENREF_60)]. Cui and colleagues showed that PM induces ROS, causing a suppression of *in vivo* proliferation in BM-MSCs[[61](#_ENREF_61)]. Moreover, more recent and higher concentrations of PM2.5 exposure in workers via welding fumes were shown to significantly reduce telomere length in HSCs[[62](#_ENREF_62)].

**OZONE**

Ozone (O3) is a highly unstable toxic gas present in low levels in the atmosphere known to cause oxidative stress. However, there has been recent mechanistic evidence to suggest that low concentrations of O3 may be therapeutic in some diseases[[63](#_ENREF_63)]. AD-MSCs exposed to high concentrations of O3 experienced cell damage via ROS, but low concentrations (5, 10 µg O3/mL) had no effect on viability. Further O3 exposure promoted adipogenesis[[64](#_ENREF_64)].

**VOCS**

VOCs are a large group of organic chemicals who disperse easily into surrounding air due to their high vapor pressure at standard air pressure. They are abundant in building materials, paints, and are produced in the burning of fossil fuels, and include third-hand smoke, the residue left behind on surfaces after smoking.

Infant eosinophil/basophil progenitor cell (Eo/B) viability was positively associated with VOC exposure, which contrasted from maternal Eo/B cells, which showed few to no associations[[65](#_ENREF_65)]. This increase of HSCs in infants due to environmental exposure suggests an enhanced risk of the development of respiratory outcomes. NSCs exposed to acrolein, a VOC present in third hand smoke, experienced high rates of cytotoxicity, altered regulatory gene expression, inhibited proliferation at low doses, and cell death at high doses[[66](#_ENREF_66)].

Formaldehyde (FA), a VOC commonly found in building materials and paints, significantly reduced nucleated bone marrow cells, and increased apoptosis in HSCs. These results suggest that FA’s toxic effects operate by altering myeloid progenitor growth and survival through oxidative damage and reduced gene expression levels[[67](#_ENREF_67)].

**DISCUSSION**

The figures illustrating PubMed publication counts for key environmental toxicants attempt to describe the onset and subsequent pattern of research interest. There was little interest in Pb from the 1960s until the late 80s’ and then a precipitous explosion of publications that is still climbing. The capture of the public’s attention with the water supply crisis which started in Flint, Michigan in 2014, coupled with the headline grabbing work exploring the transgenerational effects[[2](#_ENREF_2)], guarantee that Pb will remain a highly investigated toxicant for the foreseeable future. Compare now the recent onset of research on the heavy metal with an even higher ATSDR substance priority score, As. At the peak of publication number, six years ago in 2013, there was not even a twentieth of the number of publications on Pb. Hg and Cd have even fewer publications, with almost as high ATSDR substance priority scores as Pb and As. The difference is even more striking when we switch attention to publication in just the last five years. In that time, no review articles exist on the effect of Hg on SCs compared to over a 1000 on the effects of Pb.

Research on PAHs and OCs began in the late 60s’ and show an interesting hump of activity peaking in the late 90s’ followed by another peak in 2012-2013. BPA has only very recently begun to capture public attention and we confidently predict a steep increase in publications over the next few years. It is less clear why the dioxins on which research has existed for longer has yet to see an increase in publication activity.

Publications on the effects of alcohol on SC populations began in the 50s and show a broadly similar increase to that of Pb until a peak in 2015. More surprising is that the research on tobacco smoking garners only a tenth of the publications of alcohol in spite of constant public attention to the deleterious effects, with research appearing to have plateaued as of 2013. No reviews have been published on the effects of O3 or VOCs on SCs in the last five years. To further emphasize the disparity in publication activity, Figure 4 plots the number of PubMed Original Research Articles published between January 2014 to June 2019 against the toxicant’s ATSDR substance priority score. The regression line hopefully helps indicate those substances that are under-researched.

There are a number of reasons that contribute to the disparity including, but not limited to: Difficulty of isolation and maintenance of a given toxicant; Issues related to organic vs. inorganic form; Difficulty of administration in an *in vitro* *in vivo* preparation; and of course, obtaining of funding to pursue research on a given toxicant.

Finally, in Table 6, we consider what if any are the clear most prevalent health outcome(s) associated with each toxicant exposure and identify the most appropriate SC or SC-derived model for further research given the phase of life associated with that health outcome.

The tables of the toxicants and their effects on SCs represent a comprehensive consolidation of the references on the effects of environmental toxicants on SCs over the last five years. A note of qualification is required. It is tempting to conclude that any effect of a toxicant on a cell population is negative. Anyone who has worked in this field for any length of time likely, like one of us, has entire data sets that could not attract funding for further analysis because the interpretation of the data suggested that the “toxicant” exposure had what prima facie appeared a positive effect on the population under examination (Parker, Unpub. Obsn.)[[68](#_ENREF_68)]. However, it is important to note that, for example, an increase in proliferation in a cell population does not necessarily mean the exposure’s effect is beneficial. The result without a proper developmental investigation defies proper interpretation. But for the purposes of this review, and for the field of toxicology, that the toxicant has an effect at a level that can be reasonably be expected to be experienced by the target tissues is sufficient to indicate that the toxicant requires further study.

One of the major challenges to environmental toxicology today is quantifying the joint impact of environmental mixtures on health outcomes to more closely resemble real-world exposure[[69](#_ENREF_69)]. We have tried to be as structured as possible in our classifications and groupings but inevitably certain of our “environmental toxicants” are themselves a mixture of active ingredients. An excellent recent review on the suitability of *in vitro* SC preparation for high throughput screening of mixtures was published by Liu *et al*[[70](#_ENREF_70)].

A relatively recently acknowledged challenge is studying the combined effects of chemical and social stressors[[71](#_ENREF_71)]. Such issues appear to be a problem not tractable by an *in vitro* cell preparation. However, one can imagine comparing cell samples obtained from carefully selected subject populations to begin to ask questions of how socioeconomic status, proximity to industrial pollutants, and occupation, affects response to a subsequent stressor. Further, how cells obtained from subjects during specific stages of life may usefully inform particular risk.

Finally, the effects of radiation and SC populations rightly have focused on the role of radiation in the treatment of patients with cancer. However, particularly as attention shifts again to exploration of low earth orbit travel and beyond, researchers are turning their attention to how such travel and potential settlement will affect human physiology[[72](#_ENREF_72),[73](#_ENREF_73)].

Almeida-Porada *et al*[[74](#_ENREF_74)] explored how the effects of radiation on the bone marrow niche can negatively impact hematopoiesis due to changes in MSC function independently of direct effect on HSCs.

It is worth emphasizing that our intent is not to say that all environmental toxicant effects on human health are mediated by SCs. But understanding the effects, or lack thereof, are an important part of the process of determining mechanism, and potential interventions to ameliorate or prevent deleterious health impacts of exposure. Such models might in this regard be the “canary in the coal mine” as a more sensitive test for toxicity than other cell populations, *e.g.*, fibroblasts[[75](#_ENREF_75)]. In this direction, Liang, Yin, and Faiola present a comprehensive review on developmental neural toxicity and environmental toxicants[[76](#_ENREF_76" \o "Liang, 2019 #106)].

Industries manufacturing chemicals have a financial and legal duty to their shareholders to develop their technologies to maximize profit. The rapidity with which new chemicals appear in our environment outpaces the ability of interested parties to test and demonstrate potential deleterious impact using existing models. SC models offer a fast and robust model that can be at least a first indicator of the need for more laborious, time consuming and resource-expensive testing.

**ACKNOWLEDGEMENTS**

We wish to thank Thomas A Kocarek for helpful discussion.

**REFERENCES**

1 **Michel** **B.** Lead, mercury, cadmium and arsenic in the environment. *Sci Total Environ* 1988; **68**: 287-288 [DOI: 10.1016/0048-9697(88)90384-1]

2 **Sen A**, Heredia N, Senut MC, Land S, Hollocher K, Lu X, Dereski MO, Ruden DM. Multigenerational epigenetic inheritance in humans: DNA methylation changes associated with maternal exposure to lead can be transmitted to the grandchildren. *Sci Rep* 2015; **5**: 14466 [PMID: 26417717 DOI: 10.1038/srep14466]

3 **Oh J**, Lee YD, Wagers AJ. Stem cell aging: mechanisms, regulators and therapeutic opportunities. *Nat Med* 2014; **20**: 870-880 [PMID: 25100532 DOI: 10.1038/nm.3651]

4 **Davila JC**, Cezar GG, Thiede M, Strom S, Miki T, Trosko J. Use and application of stem cells in toxicology. *Toxicol Sci* 2004; **79**: 214-223 [PMID: 15014205 DOI: 10.1093/toxsci/kfh100]

5 **Thomson JA**, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. Embryonic stem cell lines derived from human blastocysts. *Science* 1998; **282**: 1145-1147 [PMID: 9804556 DOI: 10.1126/science.282.5391.1145]

6 **Gutiérrez-García AK**, Flores-Kelly JM, Ortiz-Rodríguez T, Kalixto-Sánchez MA, De León-Rodríguez A. Phthalates affect the in vitro expansion of human hematopoietic stem cell. *Cytotechnology* 2019; **71**: 553-561 [PMID: 30715687 DOI: 10.1007/s10616-019-00300-x]

7 **Stoddart MJ.** Cell viability assays: Introduction. In: Methods in Molecular Biology. Humana Press, 2011: 1-6 [DOI: 10.1007/978-1-61779-108-6\_1]

8 **Sciences NIoEH.** What we study.Available from: URL: https://tools.niehs.nih.gov/topics/

9 **Agency for Toxic Substances and Disease Registry.** The ATSDR 2017 substance priority list. Available from: URL: https://www.atsdr.cdc.gov/spl/#2017spl

10 **Jonasson ME**, Afshari R. Historical documentation of lead toxicity prior to the 20th century in English literature. *Hum Exp Toxicol* 2018; **37**: 775-788 [PMID: 29076389 DOI: 10.1177/0960327117737146]

11 **Wagner PJ**, Park HR, Wang Z, Kirchner R, Wei Y, Su L, Stanfield K, Guilarte TR, Wright RO, Christiani DC, Lu Q. In Vitro Effects of Lead on Gene Expression in Neural Stem Cells and Associations between Up-regulated Genes and Cognitive Scores in Children. *Environ Health Perspect* 2017; **125**: 721-729 [PMID: 27562236 DOI: 10.1289/EHP265]

12 **Liu JT**, Chen BY, Zhang JQ, Kuang F, Chen LW. Lead exposure induced microgliosis and astrogliosis in hippocampus of young mice potentially by triggering TLR4-MyD88-NFκB signaling cascades. *Toxicol Lett* 2015; **239**: 97-107 [PMID: 26386401 DOI: 10.1016/j.toxlet.2015.09.015]

13 **Rafiei H**, Shariati M, Khayatzadeh J, Afsharnezhad S, Farhoodi M. Effects of Oral Dosage of Lead Acetate II on Osteocalcin Gene Expression in Rat Mesenchymal Stem Cells. *Rep Biochem Mol Biol* 2018; **6**: 131-136 [PMID: 29765995]

14 **Wang QQ**, Lan YF, Rehman K, Jiang YH, Maimaitiyiming Y, Zhu DY, Naranmandura H. Effect of arsenic compounds on the in vitro differentiation of mouse embryonic stem cells into cardiomyocytes. *Chem Res Toxicol* 2015; **28**: 351-353 [PMID: 25166275 DOI: 10.1021/tx500286t]

15 **Shearer JJ**, Figueiredo Neto M, Umbaugh CS, Figueiredo ML. In Vivo Exposure to Inorganic Arsenic Alters Differentiation-Specific Gene Expression of Adipose-Derived Mesenchymal Stem/Stromal Cells in C57BL/6J Mouse Model. *Toxicol Sci* 2017; **157**: 172-182 [PMID: 28206643 DOI: 10.1093/toxsci/kfx026]

16 **Graham B**, Stevens J, Wells P, Sims J, Rogers C, Leggett SS, Ekunwe S, Ndebele K. Enhancement of arsenic trioxide-mediated changes in human induced pluripotent stem cells (IPS). *Int J Environ Res Public Health* 2014; **11**: 7524-7536 [PMID: 25054231 DOI: 10.3390/ijerph110707524]

17 **Li Q**, Yang Z, Zhang P, Zhao Y, Yu X, Xue P, Shao Y, Li Q, Jia X, Zhang Q, Cheng L, He M, Zhou Z, Zhang Y. Mercury impact on hematopoietic stem cells is regulated by IFNγ-dependent bone marrow-resident macrophages in mice. *Toxicol Lett* 2018; **295**: 54-63 [PMID: 29859861 DOI: 10.1016/j.toxlet.2018.05.037]

18 **Tasneem S**, Farrell K, Lee MY, Kothapalli CR. Sensitivity of neural stem cell survival, differentiation and neurite outgrowth within 3D hydrogels to environmental heavy metals. *Toxicol Lett* 2016; **242**: 9-22 [PMID: 26621541 DOI: 10.1016/j.toxlet.2015.11.021]

19 **Wang H**, Engstrom AK, Xia Z. Cadmium impairs the survival and proliferation of cultured adult subventricular neural stem cells through activation of the JNK and p38 MAP kinases. *Toxicology* 2017; **380**: 30-37 [PMID: 28163110 DOI: 10.1016/j.tox.2017.01.013]

20 **Zhang Y**, Yu X, Sun S, Li Q, Xie Y, Li Q, Zhao Y, Pei J, Zhang W, Xue P, Zhou Z, Zhang Y. Cadmium modulates hematopoietic stem and progenitor cells and skews toward myelopoiesis in mice. *Toxicol Appl Pharmacol* 2016; **313**: 24-34 [PMID: 27771405 DOI: 10.1016/j.taap.2016.10.016]

21 **Kabir ER**, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. *Environ Toxicol Pharmacol* 2015; **40**: 241-258 [PMID: 26164742 DOI: 10.1016/j.etap.2015.06.009]

22 **Alegbeleye OO**, Opeolu BO, Jackson VA. Polycyclic Aromatic Hydrocarbons: A Critical Review of Environmental Occurrence and Bioremediation. *Environ Manage* 2017; **60**: 758-783 [PMID: 28573478 DOI: 10.1007/s00267-017-0896-2]

23 **Slotkin TA**, Skavicus S, Card J, Giulio RT, Seidler FJ. In vitro models reveal differences in the developmental neurotoxicity of an environmental polycylic aromatic hydrocarbon mixture compared to benzo[a]pyrene: Neuronotypic PC12 Cells and embryonic neural stem cells. *Toxicology* 2017; **377**: 49-56 [PMID: 28049045 DOI: 10.1016/j.tox.2016.12.008]

24 **Zhou Y**, Jiang R, An L, Wang H, Cheng S, Qiong S, Weng Y. Benzo[a]pyrene impedes self-renewal and differentiation of mesenchymal stem cells and influences fracture healing. *Sci Total Environ* 2017; **587-588**: 305-315 [PMID: 28249752 DOI: 10.1016/j.scitotenv.2017.02.152]

25 **O'Brien JM**, Beal MA, Yauk CL, Marchetti F. Benzo(a)pyrene Is Mutagenic in Mouse Spermatogonial Stem Cells and Dividing Spermatogonia. *Toxicol Sci* 2016; **152**: 363-371 [PMID: 27208087 DOI: 10.1093/toxsci/kfw088]

26 **Rathore K**, Cekanova M. Effects of environmental carcinogen benzo(a)pyrene on canine adipose-derived mesenchymal stem cells. *Res Vet Sci* 2015; **103**: 34-43 [PMID: 26679793 DOI: 10.1016/j.rvsc.2015.09.012]

27 **Chiu CY**, Yen YP, Tsai KS, Yang RS, Liu SH. Low-dose benzo(a)pyrene and its epoxide metabolite inhibit myogenic differentiation in human skeletal muscle-derived progenitor cells. *Toxicol Sci* 2014; **138**: 344-353 [PMID: 24431215 DOI: 10.1093/toxsci/kfu003]

28 **Pamies D**, Sogorb MA, Fabbri M, Gribaldo L, Collotta A, Scelfo B, Vilanova E, Harris G, Bal-Price A. Genomic and phenotypic alterations of the neuronal-like cells derived from human embryonal carcinoma stem cells (NT2) caused by exposure to organophosphorus compounds paraoxon and mipafox. *Int J Mol Sci* 2014; **15**: 905-926 [PMID: 24413757 DOI: 10.3390/ijms15010905]

29 **Food and Drug Administration.** Indirect food additives: Polymers. Available from: URL: https://www.federalregister.gov/documents/2012/07/17/2012-17366/indirect-food-additives-polymers

30 **Clément F**, Xu X, Donini CF, Clément A, Omarjee S, Delay E, Treilleux I, Fervers B, Le Romancer M, Cohen PA, Maguer-Satta V. Long-term exposure to bisphenol A or benzo(a)pyrene alters the fate of human mammary epithelial stem cells in response to BMP2 and BMP4, by pre-activating BMP signaling. *Cell Death Differ* 2017; **24**: 155-166 [PMID: 27740625 DOI: 10.1038/cdd.2016.107]

31 **Prins GS**, Hu WY, Xie L, Shi GB, Hu DP, Birch L, Bosland MC. Evaluation of Bisphenol A (BPA) Exposures on Prostate Stem Cell Homeostasis and Prostate Cancer Risk in the NCTR-Sprague-Dawley Rat: An NIEHS/FDA CLARITY-BPA Consortium Study. *Environ Health Perspect* 2018; **126**: 117001 [PMID: 30387366 DOI: 10.1289/EHP3953]

32 **Li J**, Phadnis-Moghe AS, Crawford RB, Kaminski NE. Aryl hydrocarbon receptor activation by 2,3,7,8-tetrachlorodibenzo-p-dioxin impairs human B lymphopoiesis. *Toxicology* 2017; **378**: 17-24 [PMID: 28049042 DOI: 10.1016/j.tox.2016.12.010]

33 **Ahrenhoerster LS**, Tate ER, Lakatos PA, Wang X, Laiosa MD. Developmental exposure to 2,3,7,8 tetrachlorodibenzo-p-dioxin attenuates capacity of hematopoietic stem cells to undergo lymphocyte differentiation. *Toxicol Appl Pharmacol* 2014; **277**: 172-182 [PMID: 24709672 DOI: 10.1016/j.taap.2014.03.020]

34 **Laiosa MD**, Tate ER, Ahrenhoerster LS, Chen Y, Wang D. Effects of Developmental Activation of the Aryl Hydrocarbon Receptor by 2,3,7,8-Tetrachlorodibenzo-p-dioxin on Long-term Self-renewal of Murine Hematopoietic Stem Cells. *Environ Health Perspect* 2016; **124**: 957-965 [PMID: 26495820 DOI: 10.1289/ehp.1509820]

35 **Tong Y**, Niu M, Du Y, Mei W, Cao W, Dou Y, Yu H, Du X, Yuan H, Zhao W. Aryl hydrocarbon receptor suppresses the osteogenesis of mesenchymal stem cells in collagen-induced arthritic mice through the inhibition of β-catenin. *Exp Cell Res* 2017; **350**: 349-357 [PMID: 28007558 DOI: 10.1016/j.yexcr.2016.12.009]

36 **Wu M**, Xu L, Teng C, Xiao X, Hu W, Chen J, Tu W. Involvement of oxidative stress in di-2-ethylhexyl phthalate (DEHP)-induced apoptosis of mouse NE-4C neural stem cells. *Neurotoxicology* 2019; **70**: 41-47 [PMID: 30395871 DOI: 10.1016/j.neuro.2018.10.013]

37 **Yin N**, Liang S, Liang S, Hu B, Yang R, Zhou Q, Jiang G, Faiola F. DEP and DBP induce cytotoxicity in mouse embryonic stem cells and abnormally enhance neural ectoderm development. *Environ Pollut* 2018; **236**: 21-32 [PMID: 29414342 DOI: 10.1016/j.envpol.2018.01.035]

38 **Baker AH**, Watt J, Huang CK, Gerstenfeld LC, Schlezinger JJ. Tributyltin engages multiple nuclear receptor pathways and suppresses osteogenesis in bone marrow multipotent stromal cells. *Chem Res Toxicol* 2015; **28**: 1156-1166 [PMID: 25932594 DOI: 10.1021/tx500433r]

39 **Watt J**, Schlezinger JJ. Structurally-diverse, PPARγ-activating environmental toxicants induce adipogenesis and suppress osteogenesis in bone marrow mesenchymal stromal cells. *Toxicology* 2015; **331**: 66-77 [PMID: 25777084 DOI: 10.1016/j.tox.2015.03.006]

40 **Carson R,** Darling L, Darling L. Silent spring. Mass: Houghton Mifflin Harcourt, 1962

41 **Strong AL**, Shi Z, Strong MJ, Miller DF, Rusch DB, Buechlein AM, Flemington EK, McLachlan JA, Nephew KP, Burow ME, Bunnell BA. Effects of the endocrine-disrupting chemical DDT on self-renewal and differentiation of human mesenchymal stem cells. *Environ Health Perspect* 2015; **123**: 42-48 [PMID: 25014179 DOI: 10.1289/ehp.1408188]

42 **Troisi R**, Hatch EE, Titus L, Strohsnitter W, Gail MH, Huo D, Adam E, Robboy SJ, Hyer M, Hoover RN, Palmer JR. Prenatal diethylstilbestrol exposure and cancer risk in women. *Environ Mol Mutagen* 2019; **60**: 395-403 [PMID: 29124779 DOI: 10.1002/em.22155]

43 **Habas K**, Brinkworth MH, Anderson D. Diethylstilbestrol induces oxidative DNA damage, resulting in apoptosis of spermatogonial stem cells in vitro. *Toxicology* 2017; **382**: 117-121 [PMID: 28315349 DOI: 10.1016/j.tox.2017.03.013]

44 **Baars AJ**, Bakker MI, Baumann RA, Boon PE, Freijer JI, Hoogenboom LA, Hoogerbrugge R, van Klaveren JD, Liem AK, Traag WA, de Vries J. Dioxins, dioxin-like PCBs and non-dioxin-like PCBs in foodstuffs: occurrence and dietary intake in The Netherlands. *Toxicol Lett* 2004; **151**: 51-61 [PMID: 15177640 DOI: 10.1016/j.toxlet.2004.01.028]

45 **Ali I**, Julin B, Glynn A, Högberg J, Berglund M, Johansson JE, Andersson SO, Andrén O, Giovannucci E, Wolk A, Stenius U, Åkesson A. Exposure to polychlorinated biphenyls and prostate cancer: population-based prospective cohort and experimental studies. *Carcinogenesis* 2016; **37**: 1144-1151 [PMID: 27742691 DOI: 10.1093/carcin/bgw105]

46 **Pierucci F**, Frati A, Squecco R, Lenci E, Vicenti C, Slavik J, Francini F, Machala M, Meacci E. Non-dioxin-like organic toxicant PCB153 modulates sphingolipid metabolism in liver progenitor cells: its role in Cx43-formed gap junction impairment. *Arch Toxicol* 2017; **91**: 749-760 [PMID: 27318803 DOI: 10.1007/s00204-016-1750-7]

47 **Seo SH**, Son MH, Choi SD, Lee DH, Chang YS. Influence of exposure to perfluoroalkyl substances (PFASs) on the Korean general population: 10-year trend and health effects. *Environ Int* 2018; **113**: 149-161 [PMID: 29425899 DOI: 10.1016/j.envint.2018.01.025]

48 **Steves AN**, Turry A, Gill B, Clarkson-Townsend D, Bradner JM, Bachli I, Caudle WM, Miller GW, Chan AWS, Easley CA 4th. Per- and polyfluoroalkyl substances impact human spermatogenesis in a stem-cell-derived model. *Syst Biol Reprod Med* 2018; **64**: 225-239 [PMID: 29911897 DOI: 10.1080/19396368.2018.1481465]

49 **Shao L**, Luo Y, Zhou D. Hematopoietic stem cell injury induced by ionizing radiation. *Antioxid Redox Signal* 2014; **20**: 1447-1462 [PMID: 24124731 DOI: 10.1089/ars.2013.5635]

50 **Xu G**, Wu H, Zhang J, Li D, Wang Y, Wang Y, Zhang H, Lu L, Li C, Huang S, Xing Y, Zhou D, Meng A. Metformin ameliorates ionizing irradiation-induced long-term hematopoietic stem cell injury in mice. *Free Radic Biol Med* 2015; **87**: 15-25 [PMID: 26086617 DOI: 10.1016/j.freeradbiomed.2015.05.045]

51 **Gläser K**, Rohland M, Kleine-Ostmann T, Schrader T, Stopper H, Hintzsche H. Effect of Radiofrequency Radiation on Human Hematopoietic Stem Cells. *Radiat Res* 2016; **186**: 455-465 [PMID: 27710704 DOI: 10.1667/RR14405.1]

52 **Garaycoechea JI**, Crossan GP, Langevin F, Mulderrig L, Louzada S, Yang F, Guilbaud G, Park N, Roerink S, Nik-Zainal S, Stratton MR, Patel KJ. Alcohol and endogenous aldehydes damage chromosomes and mutate stem cells. *Nature* 2018; **553**: 171-177 [PMID: 29323295 DOI: 10.1038/nature25154]

53 **Lu R**, Voigt RM, Zhang Y, Kato I, Xia Y, Forsyth CB, Keshavarzian A, Sun J. Alcohol Injury Damages Intestinal Stem Cells. *Alcohol Clin Exp Res* 2017; **41**: 727-734 [PMID: 28195397 DOI: 10.1111/acer.13351]

54 **Serio RN**, Laursen KB, Urvalek AM, Gross SS, Gudas LJ. Ethanol promotes differentiation of embryonic stem cells through retinoic acid receptor-γ. *J Biol Chem* 2019; **294**: 5536-5548 [PMID: 30737277 DOI: 10.1074/jbc.RA118.007153]

55 **Lariscy JT**, Hummer RA, Rogers RG. Cigarette Smoking and All-Cause and Cause-Specific Adult Mortality in the United States. *Demography* 2018; **55**: 1855-1885 [PMID: 30232778 DOI: 10.1007/s13524-018-0707-2]

56 **Yanbaeva DG**, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. *Chest* 2007; **131**: 1557-1566 [PMID: 17494805 DOI: 10.1378/chest.06-2179]

57 **Wahl EA**, Schenck TL, Machens HG, Egaña JT. Acute stimulation of mesenchymal stem cells with cigarette smoke extract affects their migration, differentiation, and paracrine potential. *Sci Rep* 2016; **6**: 22957 [PMID: 26976359 DOI: 10.1038/srep22957]

58 **Shaito A**, Saliba J, Husari A, El-Harakeh M, Chhouri H, Hashem Y, Shihadeh A, El-Sabban M. Electronic Cigarette Smoke Impairs Normal Mesenchymal Stem Cell Differentiation. *Sci Rep* 2017; **7**: 14281 [PMID: 29079789 DOI: 10.1038/s41598-017-14634-z]

59 **Assadollahi V**, Mohammadi E, Fathi F, Hassanzadeh K, Erfan MBK, Soleimani F, Banafshi O, Yosefi F, Allahvaisi O. Effects of cigarette smoke condensate on proliferation and pluripotency gene expression in mouse embryonic stem cells. *J Cell Biochem* 2019; **120**: 4071-4080 [PMID: 30269371 DOI: 10.1002/jcb.27692]

60 **Kumar M**, Singh RS, Banerjee T. Associating airborne particulates and human health: Exploring possibilities: Comment on: Kim, Ki-Hyun, Kabir, E. and Kabir, S. 2015. A review on the human health impact of airborne particulate matter. Environment International 74 (2015) 136-143. *Environ Int* 2015; **84**: 201-202 [PMID: 26093957 DOI: 10.1016/j.envint.2015.06.002]

61 **Cui Y**, Jia F, He J, Xie X, Li Z, Fu M, Hao H, Liu Y, Liu DZ, Cowan PJ, Zhu H, Sun Q, Liu Z. Ambient Fine Particulate Matter Suppresses In Vivo Proliferation of Bone Marrow Stem Cells through Reactive Oxygen Species Formation. *PLoS One* 2015; **10**: e0127309 [PMID: 26058063 DOI: 10.1371/journal.pone.0127309]

62 **Wong JY**, De Vivo I, Lin X, Christiani DC. Cumulative PM(2.5) exposure and telomere length in workers exposed to welding fumes. *J Toxicol Environ Health A* 2014; **77**: 441-455 [PMID: 24627998 DOI: 10.1080/15287394.2013.875497]

63 **Sagai M**, Bocci V. Mechanisms of Action Involved in Ozone Therapy: Is healing induced via a mild oxidative stress? *Med Gas Res* 2011; **1**: 29 [PMID: 22185664 DOI: 10.1186/2045-9912-1-29]

64 **Costanzo M**, Boschi F, Carton F, Conti G, Covi V, Tabaracci G, Sbarbati A, Malatesta M. Low ozone concentrations promote adipogenesis in human adipose-derived adult stem cells. *Eur J Histochem* 2018; **62** [PMID: 30176704 DOI: 10.4081/ejh.2018.2969]

65 **Hörnig F**, Kohajda T, Röder S, Herberth G, von Bergen M, Borte M, Diez U, Rolle-Kampczyk U, Simon JC, Denburg JA, Lehmann I, Junge KM. The LINA Study: Higher Sensitivity of Infant Compared to Maternal Eosinophil/Basophil Progenitors to Indoor Chemical Exposures. *J Environ Public Health* 2016; **2016**: 5293932 [PMID: 27313631 DOI: 10.1155/2016/5293932]

66 **Bahl V**, Weng NJ, Schick SF, Sleiman M, Whitehead J, Ibarra A, Talbot P. Cytotoxicity of Thirdhand Smoke and Identification of Acrolein as a Volatile Thirdhand Smoke Chemical That Inhibits Cell Proliferation. *Toxicol Sci* 2016; **150**: 234-246 [PMID: 26719373 DOI: 10.1093/toxsci/kfv327]

67 **Wei C**, Wen H, Yuan L, McHale CM, Li H, Wang K, Yuan J, Yang X, Zhang L. Formaldehyde induces toxicity in mouse bone marrow and hematopoietic stem/progenitor cells and enhances benzene-induced adverse effects. *Arch Toxicol* 2017; **91**: 921-933 [PMID: 27339418 DOI: 10.1007/s00204-016-1760-5]

68 **Vangipuram SD**, Grever WE, Parker GC, Lyman WD. Ethanol increases fetal human neurosphere size and alters adhesion molecule gene expression. *Alcohol Clin Exp Res* 2008; **32**: 339-347 [PMID: 18162078 DOI: 10.1111/j.1530-0277.2007.00568.x]

69 **Bellavia A**, James-Todd T, Williams PL. Approaches for incorporating environmental mixtures as mediators in mediation analysis. *Environ Int* 2019; **123**: 368-374 [PMID: 30572168 DOI: 10.1016/j.envint.2018.12.024]

70 **Liu S**, Yin N, Faiola F. Prospects and Frontiers of Stem Cell Toxicology. *Stem Cells Dev* 2017; **26**: 1528-1539 [PMID: 28874109 DOI: 10.1089/scd.2017.0150]

71 **Sexton K**, Linder SH. Cumulative risk assessment for combined health effects from chemical and nonchemical stressors. *Am J Public Health* 2011; **101 Suppl 1**: S81-S88 [PMID: 21551386 DOI: 10.2105/AJPH.2011.300118]

72 **Blaber EA**, Parker GC. Special Issue: Stem Cells and Microgravity. *Stem Cells Dev* 2018; **27**: 783-786 [PMID: 29882739 DOI: 10.1089/scd.2018.29001.bla]

73 **Blaber EA**. Special Issue: Stem Cells, Radiation, and Microgravity. *Stem Cells Dev* 2018; **27**: 1227-1229 [PMID: 30212289 DOI: 10.1089/scd.2018.29003.bla]

74 **Almeida-Porada G**, Rodman C, Kuhlman B, Brudvik E, Moon J, George S, Guida P, Sajuthi SP, Langefeld CD, Walker SJ, Wilson PF, Porada CD. Exposure of the Bone Marrow Microenvironment to Simulated Solar and Galactic Cosmic Radiation Induces Biological Bystander Effects on Human Hematopoiesis. *Stem Cells Dev* 2018; **27**: 1237-1256 [PMID: 29698131 DOI: 10.1089/scd.2018.0005]

75 **Laschinski G**, Vogel R, Spielmann H. Cytotoxicity test using blastocyst-derived euploid embryonal stem cells: a new approach to in vitro teratogenesis screening. *Reprod Toxicol* 1991; **5**: 57-64 [PMID: 1807538]

76 **Liang S**, Yin N, Faiola F. Human Pluripotent Stem Cells as Tools for Predicting Developmental Neural Toxicity of Chemicals: Strategies, Applications, and Challenges. *Stem Cells Dev* 2019; **28**: 755-768 [PMID: 30990109 DOI: 10.1089/scd.2019.0007]

77 **Senut MC**, Sen A, Cingolani P, Shaik A, Land SJ, Ruden DM. Lead exposure disrupts global DNA methylation in human embryonic stem cells and alters their neuronal differentiation. *Toxicol Sci* 2014; **139**: 142-161 [PMID: 24519525 DOI: 10.1093/toxsci/kfu028]

78 **Bain LJ**, Liu JT, League RE. Arsenic inhibits stem cell differentiation by altering the interplay between the Wnt3a and Notch signaling pathways. *Toxicol Rep* 2016; **3**: 405-413 [PMID: 27158593 DOI: 10.1016/j.toxrep.2016.03.011]

79 **Leem YH**, Oh S, Kang HJ, Kim JH, Yoon J, Chang JS. BPA-toxicity via superoxide anion overload and a deficit in β-catenin signaling in human bone mesenchymal stem cells. *Environ Toxicol* 2017; **32**: 344-352 [PMID: 26822619 DOI: 10.1002/tox.22239]

80 **Angelos MG**, Ruh PN, Webber BR, Blum RH, Ryan CD, Bendzick L, Shim S, Yingst AM, Tufa DM, Verneris MR, Kaufman DS. Aryl hydrocarbon receptor inhibition promotes hematolymphoid development from human pluripotent stem cells. *Blood* 2017; **129**: 3428-3439 [PMID: 28533309 DOI: 10.1182/blood-2016-07-730440]

81 **Li J**, Bhattacharya S, Zhou J, Phadnis-Moghe AS, Crawford RB, Kaminski NE. Aryl Hydrocarbon Receptor Activation Suppresses EBF1 and PAX5 and Impairs Human B Lymphopoiesis. *J Immunol* 2017; **199**: 3504-3515 [PMID: 28978690 DOI: 10.4049/jimmunol.1700289]

**P-Reviewer:** Tanabe S **S-Editor:** Dou Y **L-Editor: E-Editor:**

**Specialty type:** Cell and tissue engineering

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 Toxicants and their highest rank on the 2017 ATSDR substance priority list1**

|  |  |  |
| --- | --- | --- |
| **Toxicant** | **Rank of highest scored class member** | **ATSDR score** |
| Heavy metals: |
| Lead (Pb)  | 2 | 1531 |
| Arsenic | 1 | 1674 |
| Mercury | 3 | 1458 |
| Cadmium | 7 | 1320 |
| EDs: |
| PAHs | 8 | 1306 |
| OCs | 37 | 1049 |
| BPA | Not Rated | - |
| Dioxins | 72 | 941 |
| Phthalates | 58 | 995 |
| Organotins | Not Rated | - |
| DDT | 13 | 1183 |
| DES | Not Rated | - |
| PCBs | 5 | 1345 |
| PFAS | 143 | 788 |
| Other environmental toxicants: |
| Radiation | Not Rated | - |
| Alcohol | Not Rated | - |
| Tobacco Smoking | Not Rated | - |
| Particulate Matter | Not Rated | - |
| Ozone | Not Rated | - |
| VOCs | 4 | 1358 |

1 Toxicants listed in order of number of PubMed counts listed in Table 2. ATSDR: Agency for Toxic Substances and Disease Registry; EDs: Endocrine disruptors; PAHs: Polycyclic aromatic hydrocarbons; OCs: Organophosphorus compounds; BPA: Bisphenol A; DDT: Dichlorodiphenyltrichloroethane; DES: Diethylstilbestrol; PCBs: Polychlorinated biphenyls; PFAS: Per- and polyfluoroalkyl substances; PM: Particulate matter; VOCs: Volatile organic compounds.

**Table 2 Counts from PubMed1 searches from January 2014 - June 2019**

|  |  |  |  |
| --- | --- | --- | --- |
| **Toxicant** | **Total number of articles** | **Review articles** | **Original research articles** |
| Metals: |
| Lead (Pb) | 4436 | 1239 | 3197 |
| Arsenic | 108 | 11 | 97 |
| Mercury | 22 | 0 | 22 |
| Cadmium | 44 | 2 | 42 |
| EDs: |
| PAHs | 944 | 22 | 922 |
| OCs (Pesticides) | 430 | 31 | 399 |
| BPA | 84 | 15 | 69 |
| Dioxins | 44 | 9 | 35 |
| Phthalates | 36 | 2 | 34 |
| Organotins | 24 | 0 | 24 |
| DDT | 11 | 1 | 10 |
| DES | 10 | 5 | 5 |
| PCBs | 8 | 1 | 7 |
| PFAS | 2 | 0 | 2 |
| Other environmental toxicants: |
| Radiation | 4302 | 589 | 3713 |
| Alcohol | 1760 | 112 | 1648 |
| Tobacco Smoking | 188 | 34 | 154 |
| PM | 61 | 3 | 58 |
| Ozone | 17 | 0 | 17 |
| VOCs | 11 | 0 | 11 |

1PubMed.gov, the United States National Library of Medicine National Institutes of Health. ED: Endocrine disruptors; PAHs: Polycyclic aromatic hydrocarbons; OCs: Organophosphorus compounds; BPA: Bisphenol A; DDT: Dichlorodiphenyltrichloroethane; DES: Diethylstilbestrol; PCBs: Polychlorinated biphenyls; PFAS: Per- and polyfluoroalkyl substances; PM: Particulate matter; VOCs: Volatile organic compounds.

**Table 3 Heavy metals and their effects on stem cells**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Environmental Toxicant** | **Type of stem cell** | **Model** | ***In vivo*/*In vitro*** | **Parameters1** | **Reference** |
| Lead  | Fetal germ  | H | *In vivo* | ↑DNA methylation changes | [[2](#_ENREF_2)] |
| Lead  | Neural progenitor  | H | *In vitro* | ↓Proliferation | [[11](#_ENREF_11)] |
| Lead  | ESC | H | *In vitro* | ↑Neuronal differentiation changes | [[77](#_ENREF_77)] |
| Lead  | Bone marrow-derived MSC | R | *In vitro* | ↓Osteogenesis | [[13](#_ENREF_13)]  |
| Lead | Neural stem  | M | *In vitro* | ↑Astrogliogenesis, ↑Microgliosis | [[12](#_ENREF_12)] |
| Arsenic | ESC | M | *In vitro* | ↓Differentiation | [[78](#_ENREF_78)] |
| Arsenic | Adipose-derived MSC | M | *In vivo* | ↓Differentiation | [[15](#_ENREF_15)] |
| Arsenic | Induced pluripotent stem cell | H | *In vitro* | ↓Viability, ↑DNA damage | [[16](#_ENREF_16)] |
| Mercury | HSC | M | *In vivo* | ↓Proliferation at high-doses ↑Proliferation at low-doses | [[17](#_ENREF_17)]  |
| Mercury | Neural progenitor  | M | *In vivo* | ↓Differentiation | [[18](#_ENREF_18)] |
| Cadmium | Neural progenitor  | H | *In vitro* | ↓Proliferation, ↑Apoptosis | [[19](#_ENREF_19)] |
| Cadmium | HSC | M | *In vivo* | ↓Differentiation potential, ↑Myelopoiesis | [[20](#_ENREF_20)] |

1For detailed information on parameters, see text below. H: Human; R: Rat; M: Mouse; ESC: Embryonic stem cells; HSC: Hematopoietic stem cells; MSC: Mesenchymal stem cells.

**Table 4 Endocrine disruptors and their effects on stem cells**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Environmental Toxicant** | **Type of stem cell** | **Model** | ***In vivo*/*In vitro*** | **Parameters1** | **Reference** |
| PAHs | Neural progenitor | R | *In vitro* | ↑Proliferation, ↓Cell size | [[23](#_ENREF_23)] |
| PAHs | HSC | H | *In vitro* | ↓Osteoblast differentiation, ↓Self-renewal | [[24](#_ENREF_24)] |
| PAHs | Spermatogonial stem  | M | *In vivo* | ↑Mutations | [[25](#_ENREF_25)] |
| PAHs | Adipose-derived MSC | C | *In vitro* | ↓Adipocyte differentiation potential | [[26](#_ENREF_26)] |
| PAHs | Skeletal muscle-derived progenitor  | H | *In vitro* | ↓Myogenic differentiation | [[27](#_ENREF_27)] |
| OCs | Neural progenitors derived from human embryonal carcinoma stem | H | *In vitro* | ↓Viability | [[28](#_ENREF_28)] |
| Bisphenol A | Mammary epithelial stem  | H | *In vitro* | ↑Proliferation, ↑Sphere-forming capability | [[30](#_ENREF_30)] |
| Bisphenol A | Prostate epithelial stem  | R | *In vivo* | ↑Proliferation | [[31](#_ENREF_31)] |
| Bisphenol A | Bone marrow MSC | H | *In vitro* | ↑Cytotoxicity | [[79](#_ENREF_79)] |
| Dioxins  | Umbilical cord blood–derived iPSC | H | *In vitro* | ↑Differentiation | [[80](#_ENREF_80)] |
| Dioxins | Cord blood derived HSC | H | *In vitro* | ↓Lymphopoiesis | [[32](#_ENREF_32),81] |
| Dioxins  | Bone marrow MSC | M | *In vitro* | ↓Osteogenesis | [[35](#_ENREF_35)] |
| Dioxins | HSC | M | *In vivo* | ↑Cell number, ↓Lymphocyte differentiation | [[33](#_ENREF_33)] |
| Dioxins | HSC | M | *In vitro* | ↓Long-term self-renewal | [[34](#_ENREF_34)] |
| Phthalates | HSC | H | *In vitro* | ↓Viability | [[6](#_ENREF_6)] |
| Phthalates | Neural progenitor | M | *In vitro* | ↓Viability, ↑ROS, ↑Apoptosis | [[36](#_ENREF_36)] |
| Phthalates | ESC | M | *In vitro* | ↓Viability | [[37](#_ENREF_37)] |
| Organotins | Spermatogonial stem  | H | *In vitro* | ↑Apoptosis |  |
| Organotins | Bone marrow MSC | M | *In vitro* | ↑Adipogenesis, ↓Osteogenesis | [[38](#_ENREF_38)] |
| Organotins | Bone marrow MSC | M | *In vitro* | ↑Adipogenesis | [[39](#_ENREF_39)] |
| DDT | Bone marrow MSC | H | *In vitro* | ↑Proliferation, ↑Differentiation, ↓Morphological changes | [[41](#_ENREF_41)] |
| DES | Spermatogonial stem  | M | *In vitro* | ↑DNA damage, ↑Apoptosis | [[43](#_ENREF_43)] |
| PCBs | Liver epithelial stem-like  | R | *In vitro* | ↑Alterations in gene signaling | [[46](#_ENREF_46)] |
| PFAS | Spermatogonial stem  | H | *In vitro* | ↓Expression of spermatogonial markers | [[48](#_ENREF_48)] |

1For detailed information on parameters, see text below. PAHs: Polycyclic aromatic hydrocarbons; OCs: Organophosphorus compounds; BPA: Bisphenol A; DDT: Dichlorodiphenyltrichloroethane; DES: Diethylstilbestrol; HSC: Hematopoietic stem cells; MSC: Mesenchymal stem cells; iPSC: Induced pluripotent stem cells; ESC: Embryonic stem cells; PCBs: Polychlorinated biphenyls; PFAS: Per- and polyfluoroalkyl substances; H: Human; R: Rat; C: Canine; M: Mouse; ROS: Reactive oxygen species.

**Table 5 Other environmental toxicants and their effects on stem cells**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Environmental Toxicant** | **Type of stem cell** | **Model** | ***In vivo*/*In vitro*** | **Parameters1** | **Reference** |
| Radiation, Ionizing | HSC | H | *In vitro* | ↑ROS, ↑Apoptosis, ↑Senescence, ↓Long-term renewal | [49,[50](#_ENREF_50)] |
| Radiation, Radiofrequency | HSC | H | *In vitro* | ↓DNA damage | [[51](#_ENREF_51)] |
| Alcohol | HSC | M | *In vivo* | ↑DNA double stranded breaks, ↑Chromosome rearrangement, ↑Myelopoiesis | [[52](#_ENREF_52)] |
| Alcohol | Intestinal stem  | M | *In vivo* | ↓Differentiation  | [[53](#_ENREF_53)] |
| Alcohol  | ESC | H | *In vitro* | ↑Differentiation | [[54](#_ENREF_54)] |
| Cigarette smoke | ESC | M | *In vitro* | ↑Apoptosis, ↓Viability | [[59](#_ENREF_59)] |
| Cigarette smoke | Bone marrow MSC | H | *In vitro* | ↓Differentiation, ↓Morphological changes | [[58](#_ENREF_58)] |
| Particulate Matter | Bone marrow MSC | M | *In vivo* | ↑ROS, ↓Proliferation | [[61](#_ENREF_61)] |
| Particulate Matter | HSC | H | *In vivo* | ↓Telomere length | [[62](#_ENREF_62)] |
| Ozone (O3) | Adipose-derived MSC | H | *In vitro* | ↑ROS, ↑Lipid accumulation | [[64](#_ENREF_64)] |
| VOCs | Bone marrow HSC | M | *In vivo* | ↑Apoptosis, ↓Nucleated bone marrow cells | [[67](#_ENREF_67)] |
| VOCs | Enhanced eosinophil/ basophil progenitor  | H | *In vivo* | ↑Differentiation | [[65](#_ENREF_65)] |
| VOCs | Neural progenitor  | M | *In vitro* | ↑Cytotoxicity | [[66](#_ENREF_66)] |

1For detailed information on parameters, see text below. HSC: Hematopoietic stem cells; ESC: Embryonic stem cells; MSC: Mesenchymal stem cells; VOCs: Volatile organic compounds; H: Human; M: Mouse; ROS: Reactive oxygen species.

**Table 6 Proposed under-researched opportunities for stem cell models on environmental exposures**

|  |  |  |
| --- | --- | --- |
| **Environmental toxicant** | **Health outcomes** | **Stem cell model** |
| Heavy metals |
|  Pb  | Decreased child cognition | Neural progenitor and SC-derived organoids |
| Pb | Adult liver function | SC-derived organoids |
|  As | Carcinogen: all tissues | Epigenetic analysis of different tissue SC populations |
|  Hg | Cognitive function | Neural progenitor and SC-derived organoids |
|  Cd | Kidney  | Renal epithelial stem Nephron progenitor  |
|  Cd | Lung damage | Alveolar epithelial progenitor  |
|  Cd | Lower bone strength | MSC |
| Endocrine disruptors |
| PAHs | Carcinogen: lung, skin | Epigenetic analysis of different tissue SC populations |
| OCs (Pesticides) | Cognition | Neural progenitor and SC-derived organoids |
| BPA | Unclear |  |
| Dioxins | Carcinogen | Epigenetic analysis of different tissue SC populations |
| Phthalates | Carcinogen | Epigenetic analysis of different tissue SC populations |
|  | Cognition | Neural progenitor and SC-derived organoids |
| Organotins | Carcinogen | Epigenetic analysis of different tissue SC populations |
| Organotins | CNS | Neural progenitor and SC-derived organoids |
| Organotins | Liver | SC-derived organoids |
|  | Kidney | Renal epithelial stem Nephron progenitor  |
| DDT | Carcinogen | Epigenetic analysis of different tissue SC populations |
| PCBs | Immune system | HSC derived populations |
| PCBs | Carcinogen  | Epigenetic analysis of different tissue SC populations |
| PCBs | Cognition | Neural progenitor and SC-derived organoids |
| PFAS | Unclear |  |
| Other toxicants |
| Particulate matter | Unclear |  |
| Ozone | Constricted breathing | SC-derived smooth muscle |
| VOCs | Unclear |  |

PAHs: Polycyclic aromatic hydrocarbons; OCs: Organophosphorus compounds; Pb: Lead; As: Arsenic; Cd: Cadmium; Hg: Mercury; BPA: Bisphenol A; DDT: Dichlorodiphenyltrichloroethane; DES: Diethylstilbestrol; PCBs: Polychlorinated biphenyls; PFAS: Per- and polyfluoroalkyl substances; VOCs: Volatile organic compounds.

****

**Figure 1 Heavy metal PubMed publication counts from 1953 - June 2019.** A: Counts resulting from a PubMed search of the term, “Lead Pb and Stem Cells” plotted against time in years; B: Counts resulting from a PubMed search of the term, “Arsenic and Stem Cells” plotted against time in years; C: Counts resulting from a PubMed search of the term, “Mercury and Stem Cells” plotted against time in years; D: Counts resulting from a PubMed search of the term, “Cadmium and Stem Cells” plotted against time in years.

**Figure 2 Endocrine disruptor PubMed publication counts from 1953 - June 2019.** A: Counts resulting from a PubMed search of the term, “Polycyclic Aromatic Hydrocarbons and Stem Cells” plotted against time in years; B: Counts resulting from a PubMed search of the term, “Organophosphorus Compounds and Stem Cells” plotted against time in years; C: Counts resulting from a PubMed search of the term, “Bisphenol A and Stem Cells” plotted against time in years; D: Counts resulting from a PubMed search of the term, “Dioxins and Stem Cells” plotted against time in years.

**Figure 3 Other environmental toxicants PubMed publication counts from 1953 - June 2019.** A: Counts resulting from a PubMed search of the term, “Alcohol and Stem Cells” plotted against time in years; B: Counts resulting from a PubMed search of the term, “Smoking and Stem Cells” plotted against time in years; C: Counts resulting from a PubMed search of the term, “Particulate Matter and Stem Cells” plotted against time in years.

**Figure 4 Agency for toxic substances and disease registry score *vs* number of PubMed original research articles 2014 - June 2019.** ATSDR: Agency for Toxic Substances and Disease Registry; PAHs: Polycyclic Aromatic Hydrocarbons; OCs: Organophosphorus Compounds; Pb: Lead; As: Arsenic; Cd: Cadmium; Hg: Mercury; DDT: Dichlorodiphenyltrichloroethane; PCBs: Polychlorinated Biphenyls; PFAS: Per- and polyfluoroalkyl substances.