A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP9560.

Invited Perspective: Does Developmental Adaptation Pose Risks with Changing Toxicant Exposures?

Edward D. Levin[1]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA

https://doi.org/10.1289/EHP9560

Refers to https://doi.org/10.1289/EHP8795

The fields of reproductive and developmental toxicology have found a great many examples of toxicant exposures causing adverse consequences that are expressed from one generation to the next. López-Rodríguez et al. (2021) provide two important examples of how neural and endocrine toxicity can be expressed across generations, one persistent and one emergent.

They reported a persisting effect with developmental exposure to an endocrine-disrupting mixture in which an effect (reduced maternal behavior) that was present in the F1 generation was also seen in the F2 and F3 generations. Toxicant effects can persist in a variety of ways across generations, including the neural and epigenetic changes seen by these investigators. Importantly, they showed with cross-fostering studies that toxicant-induced changes in maternal care by the F1 generation caused changes in maternal care by their offspring and subsequent generations. The deficits were not apparent with cross-fostering. Thus, it appears that the persistence of the effect across generations was carried through behaviorally due to the repetition of lessened maternal care in each generation. Toxicant-induced changes in maternal and other social behavior like those in other animals can have cascading effects in humans that are relayed across generations long after the toxicant exposure has ended.

These investigators also documented an interesting case of emerging toxicity (delayed sexual maturation and follicular development in adulthood) expressed across generations. They found that that low-dose developmental exposure to a mixture of endocrine-disrupting compounds did not cause delayed sexual maturation in the F1 generation but did cause this effect in F2 and F3 generations. This is not a persistence of effect, but rather an emergence of effect across generations. This effect may be due to low-dose exposure causing adaptations in development that compensated for the exposure effects in the F1 generation but that were maladaptive in later generations when the endocrine disruption was not present.

As we advance toxicology by investigating lower-dose effects, we should consider going beyond the injury model of toxicology to also include the adaptation model. The processes of organismal development are characterized not only by the assembly of a body that can live in the environment but also the adaptation of that body to live optimally in the particular type of environment into which it is born. The evolutionary history of the organism's species provides genetic instruction for the assembly that is honed by epochs of selection for fitness in a general environment.

One set of evolved processes that can provide advantages for fitness to more specific environments is epigenetic modifications of genes. The processes of DNA methylation, histone modifications, and alterations in noncoding RNA expression during development provide ways by which expression of the genome can be modified by environmental conditions for better fitness more quickly than possible with genomic evolution. Epigenetic alterations of the gametes and the resulting developing organism from zygote to adult can sculpt physiology to be better attuned to the attributes of the specific environment in which the organism will live. Environmental characteristics such as microbial community, food availability, behavioral stress, and chemical exposures can alter development and change the direction of the lifelong function of the organism. Severe changes in these factors can cause pathology that impairs physiological function for the life of the individual. This process been studied for the most part in the field of developmental toxicology in a specialty called the developmental origins of health and disease (DOHaD) (Bianco-Miotto et al. 2017; Suzuki 2018).

There is a range of doses of these factors to which we are all exposed. Generally, the lower the dose of exposure, the fewer pathological effects seen with each individual, but these remain important because a greater proportion of the population is exposed. If the evolutionary advantage of developmental epigenetic alterations is to provide guidance for the organism to develop optimally to an environment, then less-extreme influences might provide beneficial adaptations to help the organism live well in that specific environment. This adaptation could result in a hormetic limb of the dose–effect function that would benefit the organism adapted to that environment. This form of nonmonotonic dose–effect function has received some study (Calabrese and Blain 2005).

But what has not been much studied is the possibility of "mis-adaptation" when chemical environments change over the life span of an organism. This phenomenon is similar to the environmental mismatch during development described by Gluckman et al. (2019), extended to changing chemical environments. With changing chemical environments, developmental adaptations would not prepare the organism well for the world in which it would live. There would be a mis-adaptation, and pathological effects could ensue. A nonchemical example would be an organism that developed in an environment of food scarcity and developed very efficient use of available calories. If the organism goes on to live in a food-plenty environment, it could become prone to obesity.

Our chemical environment is quite complex, but particularly in recent decades it also has become an ever-changing one. A good example of a changing chemical environment that people experience is exposure to insecticides, including organochlorines, then organophosphates, pyrethroids, and most recently neonicotinoids, each with their differing mechanisms of toxicity (Abreu-Villaça and Levin 2017). Organisms that developed in the context of exposure to organochlorine pesticides may be ill prepared to deal with later exposures to neonicotinoid pesticides. Effects of changing toxicant exposures would be relatively straightforward to test in experimental models. Certainly,

Address correspondence to Edward D. Levin, Department of Psychiatry and Behavioral Sciences, Box 104790, Duke University Medical Center, Durham, NC 27710-1000 USA. Telephone: (919) 681-6273. Email: edlevin@duke.edu

The author declares he has no actual or potential competing financial interests.

Received 27 April 2021; Revised 7 June 2021; Accepted 13 July 2021; Published 12 August 2021.

complex mixtures must be studied because that is the reality of our exposure in the environment, but we must also face the risks that of ever-changing toxicant exposures over our life spans and future generations.

Acknowledgments

E.D.L. is supported by the Duke University Superfund Research Center (ES010356).

References

Abreu-Villaça Y, Levin ED. 2017. Developmental neurotoxicity of succeeding generations of insecticides. Environ Int 99:55–77, PMID: 27908457, https://doi.org/10.1016/j.envint.2016.11.019.

Bianco-Miotto T, Craig JM, Gasser YP, van Dijk SJ, Ozanne SE. 2017. Epigenetics and DOHaD: from basics to birth and beyond. J Dev Orig Health Dis 8(5):513–519, PMID: 28889823, https://doi.org/10.1017/S2040174417000733.

Calabrese EJ, Blain R. 2005. The occurrence of hormetic dose responses in the toxicological literature, the hormesis database: an overview. Toxicol Appl Pharmacol 202(3):289–301, PMID: 15667834, https://doi.org/10.1016/j.taap.2004.06.023.

Gluckman PD, Hanson MA, Low FM. 2019. Evolutionary and developmental mismatches are consequences of adaptive developmental plasticity in humans and have implications for later disease risk. Philos Trans R Soc Lond B Biol Sci 3374(1770): 20180109, PMID: 30966891, https://doi.org/10.1098/rstb.2018.0109.

López-Rodríguez D, Aylwin CF, Delli V, Sevrin E, Campanile M, Martin M, et al. 2021. Multi- and transgenerational disruption of maternal behavior and female puberty by a mixture of endocrine disrupting chemical (EDC). Environ Health Perspect 129(8): 087003, https://doi.org/10.1289/EHP8795.

Suzuki K. 2018. The developing world of DOHaD. J Dev Orig Health Dis 9(3):266–269, PMID: 28870276, https://doi.org/10.1017/S2040174417000691.