and investment in HCV vaccine development have been inadequate, however, and such a project faces many challenges and scientific hurdles. A concerted and coordinated research effort by the public and private sectors could help achieve this goal.

Major strides have been made in understanding HCV infection and associated diseases. Yet many unmet needs and knowledge gaps remain. For instance, we still don't know enough about how HCV establishes productive infection, how it persists in an otherwise healthy person, what the mechanisms involved in an effective immune response are, which molecular and genetic changes in people with chronic HCV infection are associated with liver cancer, and how infection alters host metabolism and organ-system functions to elicit pathologic responses and disease processes. Although excellent research tools exist to study HCV infection, a convenient and relevant animal model is still needed.

An audio interview with Dr. Liang is available at NEJM.org

Current knowledge of the genetic and other determinants of HCV-related disease progression and cancer development is still rudimentary. Without a solid understanding of these processes and validated biomarkers, the goal of tailoring treatment to individual patients' needs will remain elusive. Despite the development of highly effective medications, many treatment challenges persist. People infected with HCV genotype 3 and people with liver cirrhosis are least likely to have a response to treatment. Drug resistance can emerge in patients with multiple treatment failures, and there is theoretical concern regarding the spread of multidrug-resistant HCV in such patients, especially among injection-drug users. Thus, many important questions pertaining to hepatitis C remain, and more research investments are needed to find the answers.

The opioid epidemic is a stark reminder of the consequences of a societal problem that remained hidden for years, in part because of the stigma associated with drug use and the reluctance to confront it as a public health problem. The concurrent spread of HCV, if not controlled, will similarly have public health and financial repercussions for decades to come.

Disclosure forms provided by the authors are available at NEJM.org.

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Polluting Developing Brains — EPA Failure on Chlorpyrifos

Virginia A. Rauh, Sc.D.

The regulatory plan developed by the U.S. Environmental Protection Agency (EPA) just before the 2016 elections was excellent: revoke all allowances for foods to contain residue of the organophosphate insecticide chlorpyrifos ("food tolerances"), essentially prohibiting agricultural and all remaining uses of the chemical. Indoor residential and some agricultural uses of chlorpyrifos had already been phased out in 2000–2001 after the EPA found the levels of exposure faced by children to be unsafe. A total ban was the logical conclusion after decades of risk assessment showing increasing evidence of threats to human health, and children's safety in particular.

Just as the EPA was poised to act, however, the plan was scrapped in March 2017 by incoming EPA Administrator Scott Pruitt, who overrode the recommendation of agency scientists to ban all commercial use of chlorpyrifos. The chemical industry and companies using this compound are pleased with the Trump administration's shift; they argue that existing chemical production will benefit from less rigid risk assessment. In reality, this action essentially violates the EPA's statutory duty to protect human health, ignoring explicit child health policy dating back to 1995 that requires all national public health standards to address the special vulnerability of infants and children.

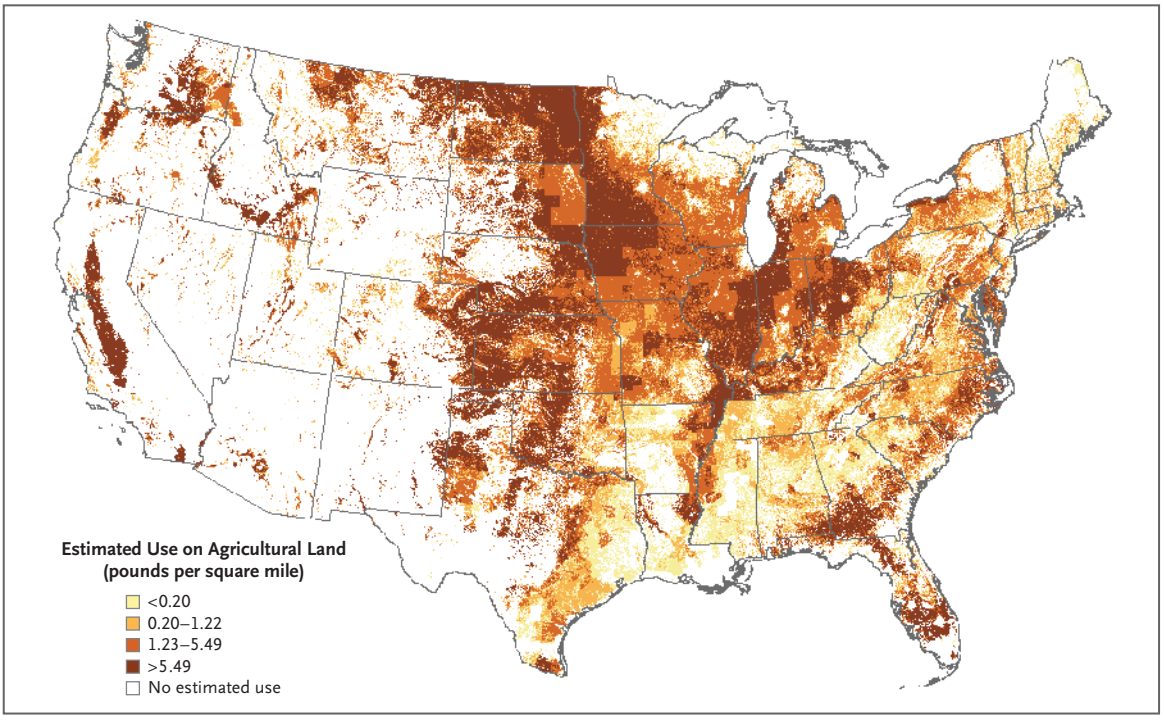
The medical community has long understood that children may be more vulnerable than adults when facing an equivalent level of exposure to a drug or other medication. Age-related differences in susceptibility to chemicals, and the particular vulnerability of very young children, reflect the delicate processes that accompany organ development and the lack of physiologic maturity. There are also age-related differences in levels of exposure to chemicals found in the environment; per unit of body weight, children eat more food and drink more water — both potential sources of exposure. They also breathe more rapidly and may inhale more of an air pollutant per pound of body weight than adults. Documentation of the differences between children and adults is integral to Food and Drug Administration assessments of drug safety; it seems reasonable to apply this approach to determinations of the safety of nonmedicinal environmental chemicals as well.

Harmful effects of chlorpyrifos on the developing brain are hardly surprising, given that this chemical was initially developed to attack the nervous system by inhibiting neurotransmitters in the body. First introduced as nerve-gas agents during World War II, organophosphate chemicals were later repurposed by chemical companies as insecticides and other pesticides. All organophosphates produce systemic toxic effects by inhibiting acetylcholinesterase (AChE), causing symptoms of cholinergic hyperstimulation. Because these effects were assumed to be the common mechanism producing neurodevelopmental deficits, the EPA has used the guidelines for detecting AChE inhibition to set human safety limits. However, studies in animals and more recent studies in humans clearly show that organophosphate chemicals are developmental neurotoxicants even at exposure levels below the threshold for systemic toxicity due to AChE inhibition. The results of these studies implicate other pathogenic mechanisms involving widespread disruption of neural cell replication and differentiation, axonogenesis and synaptogenesis, and synaptic function.[1] In light of such mechanisms, all related to processes required for later cognitive and behavioral tasks, there is good reason to be concerned about possible longer-term, potentially irreversible effects. Therefore, human-exposure limits based on the detection of cholinesterase inhibition are likely to be insufficient to protect brain development.

Among the most worrisome findings are the corroborative results from several prospective cohort studies of children, which show an inverse dose–response effect of prenatal exposure to chlorpyrifos on cognition at 7 years of age.[2] In a subgroup of inner-city children 5.9 to 11.2 years of age from one of the cohorts, magnetic resonance imaging revealed structural anomalies in the brains of the most highly exposed children in the superior temporal, posterior middle temporal, and inferior postcentral gyri bilaterally, and in the superior frontal gyrus, gyrus rectus, cuneus, and precuneus along the mesial wall of the right hemisphere.[3] Cognitive and behavioral processes subserved by these cortical regions include attention, receptive language, social cognition, reward, emotion, and inhibitory control; complementary functional deficits were also observed in a number of auditory attention skills. Deformations were detected in the dorsal and mesial surfaces of the left superior frontal gyrus, which supports executive function — a critical set of mental skills that permit people to plan, organize, and complete tasks throughout life.

In fact, one review (assuming a population of 25.5 million children 0 to 5 years of age in the United States) calculates a total loss of 16.9 million IQ points due to exposure to organophosphates, of which chlorpyrifos is the most widely used.[4] Such an estimate is staggering and yet does not begin to capture the full range of economic and health-related costs potentially associated with this toxic exposure. For example, there is recent and growing evidence of persistent motor deficits among children with high early exposure to chlorpyrifos.[5] Because adult occupational exposures to chlorpyrifos have been clearly linked to Parkinson's disease, there is good reason to worry that early exposures may set in motion a pathogenic trajectory potentially leading to neurodegenerative disease. On the basis of this brief review of the evidence, it would be difficult to conclude that chlorpyrifos poses no threat to the long-term health and development of infants and children.

The EPA, charged with protecting human health and the environment, regulates some 80,000 different chemicals used in workplaces, homes, and everyday products — many of them highly toxic. After the 2000–2001 phase-out of indoor residential use, the agency planned to further restrict agricultural applications of chlorpyrifos, which was still widely used on fruits and vegetables, including apples, almonds, and dozens of other crops (see map). Unable to definitively establish the safety of chlorpyrifos on the basis of the available science, the EPA



Estimated Agricultural Use for Chlorpyrifos, 2015 (Preliminary).

Estimates are from the U.S. Geological Survey National Water-Quality Assessment Project. For all states except California, the map shows high estimates of pesticide use (EPest-high). EPest-high includes more extensive estimates of pesticide use not reported in surveys, which sometimes include states or areas where use restrictions have been imposed. When a crop reporting district (CRD) is surveyed and pesticide use is not reported for a particular crop present in the CRD, the EPest-high treats the unreported use for that pesticide-by-crop combination in the CRD as missing data, and pesticide-by-crop use rates from neighboring CRDs or CRDs within the same region are used to estimate the pesticide-by-crop rate for the CRD. State-based restrictions on pesticide use were not incorporated into estimates.

initially proposed in 2015 to revoke all food residue tolerances; it later revised this proposal to focus specifically on risks from dietary exposure and drinking water, important sources of children's organophosphate pesticide exposure. Unfortunately, this policy did not go into effect, which set the stage for the current regulatory breakdown.

Ultimately, regulatory action should reduce risks and achieve equity — a fair distribution of the costs and benefits of such action across segments of society. Yet the history of environmental pollution in the United States reveals a regulatory problem in which the real costs of pollution are frequently borne by people who are outside the market: they are neither the producers (the chemical companies) nor the consumers (the growers), and yet they are negatively affected by the product. The imperfect alignment of industry interests with regulatory and public health interests has been known to result in industry's failure to reveal known health risks and efforts to discredit the scientific evidence linking exposure with negative health outcomes. The resulting lack of regulatory action is thus compatible with industry's interests and misaligned with the public health.

In the case of chlorpyrifos, the heaviest burden of ambient exposure is borne by families in farming communities, many of whom are low-income Latino and migrant workers. In some agricultural areas, levels of organophosphates in the urinary metabolites of pregnant women are actually higher than levels before the initial indoor residential ban, indicating that the EPA has failed to achieve a fair and equitable distribution of risk across populations.

Despite the growing body of scientific evidence suggesting otherwise, current regulatory policy would lead the public to believe that, under conditions of normal use, chlorpyrifos is not harmful to pregnant women and children. The EPA is required by federal law to ban or regulate a chemical if it cannot prove with reasonable certainty that the chemical is safe. In the case of chlorpyrifos, it has failed to provide this certainty. As a result, it may be putting an entire generation of young brains in harm's way.

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Rethinking Criminalization of HIV Exposure — Lessons from California's New Legislation

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Laws that criminalize certain behaviors on the basis of the person's HIV status have long been challenged as ineffective prevention measures that harm public health. They are nevertheless widespread: according to the Center for HIV Law and Policy, 34 states have HIV-specific criminal statutes, and 23 have applied more general laws (e.g., against assault with a deadly weapon) in order to criminalize HIV exposure. Most of these laws don't reflect current evidence regarding protective factors such as antiretroviral treatment (ART), and many encompass behaviors that carry negligible risk.

California is now breaking from these precedents. In October 2017, Governor Jerry Brown signed SB 239, which reduces the criminal charges associated with exposing a sexual partner to HIV without disclosing one's HIV status. In place of former felony charges, California will impose misdemeanor charges that carry a maximum of 6 months of jail time and will reserve penalties for intentional disease transmission. The law also repeals felony charges for solicitation (prostitution) by people who have tested positive for HIV, and it decriminalizes their donation of blood or tissue.

The strongest arguments for criminalizing HIV exposure emphasize two functions of criminal law: retribution and deterrence. But emerging evidence casts doubt on both those justifications. The justification for criminalizing HIV exposure for the purpose of retribution is that such behavior is morally blameworthy. If we follow this rationale, the defendant's state of mind is important. Most HIV-specific statutes, however, omit intent to infect as a condition of the offense — simply being aware of one's HIV status is enough to warrant a penalty. Such laws also do little to differentiate among reasons for nondisclosure (e.g., fears of partner violence, or economic necessity for sex workers), and they often impose heavy penalties for conduct that poses slim risks of infection or about which there is substantial moral ambiguity.[1] Retribution is particularly inappropriate for behaviors that have virtually no capacity to transmit infection, and prevention tools for HIV-positive people (e.g., ART) have reclassified many activities as lower risk.

Evidence also indicates that penalties associated with HIV-specific statutes are unevenly imposed on the basis of race and sex. In California, for example, black and Latino people compose half the population of people with HIV but two thirds of defendants in HIV-criminalization cases; black women, in particular, account for only 4% of the state's HIV-positive population but 21% of these cases.[2] Moreover, among people arrested for HIV-related crimes, white men were released and not charged in 61% of incidents, as compared with 44% of incidents for black women, 39% for white women, and 38% for black men. Discriminatory enforcement of HIV-criminalization statutes compounds injustices based on race, sex, and socioeconomic status, and it undermines the retributivist rationale for HIV criminalization.

Judged against the goal of deterrence, HIV-specific statutes haven't been successful, and they may detract from more effective prevention efforts such as advances in treatment and blood-supply screening. Past analyses have found that neither the presence of an HIV-criminalization statute nor people's awareness of it affects their views regarding responsibility for HIV transmission.[1] These statutes therefore may not affect moral calculations for people mak-