Published in final edited form as:

Bioethics. 2015 March ; 29(3): 182–189. doi:10.1111/bioe.12079.

Bisphenol A and Risk Management Ethics

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Abstract

It is widely recognized that endocrine disrupting compounds, such as Bisphenol A, pose challenges for traditional paradigms in toxicology, insofar as these substances appear to have a wider range of low-dose effects than previously recognized. These compounds also pose challenges for ethics and policymaking. When a chemical does not have significant low-dose effects, regulators can allow it to be introduced into commerce or the environment, provided that procedures and rules are in place to keep exposures below an acceptable level. This option allows society to maximize the benefits from the use of the chemical while minimizing risks to human health or the environment, and it represents a compromise between competing values. When it is not possible to establish acceptable exposure levels for chemicals that pose significant health or environmental risks, the most reasonable options for risk management may be to enact either partial or complete bans on their use. These options create greater moral conflict than other risk management strategies, leaving policymakers difficult choices between competing values.

Keywords

Bisphenol A; risk management; ethics; regulation; low dose effects; endocrine disruptors

The Bisphenol A Controversy

Bisphenol A (BPA), a chemical used to make polycarbonate plastics and epoxy resins, has been at the center of a storm of scientific and political controversy in the last decade.¹ BPA can be found in some types of water and infant bottles, compact discs, computers, toys, medical devices, kitchen appliances, linings for food cans and water supply pipes, bottle tops, papers, and dental sealants.^{2,3} Each year, manufacturers around the globe produce more than eight billion pounds of BPA, which makes it one of the most common industrial chemicals.⁴ Most of the human exposure to BPA occurs through the diet, when the chemical leaches out from food or beverage containers. Exposure to the chemical is widespread—BPA has been detected in human blood, urine, milk, saliva, and amniotic fluid—and there is considerable concern that it may cause adverse health effects even at low doses, i.e., less than 5 mg per kg body weight per day.⁵ In the 1980s, the Environmental Protection Agency (EPA) determined that a BPA dose below 50 mg per kg of body weight per day is safe, but evidence from various studies challenges this assumption.^{6,7} Since BPA does not persist in the environment or bioaccumulate, human exposure should diminish if BPA use is reduced.⁸

Since the 1990s, hundreds of studies have examined the effects of BPA on physiology, behavior, and development in animals.⁹ Far fewer studies have examined BPA's effects in humans.¹⁰ BPA is considered to be an endocrine disrupting compound because it can interfere with the proper functioning of hormones in the body. At low doses, BPA binds with estrogen receptors, and at higher doses it impedes androgen receptors.¹¹ When BPA binds with a receptor, it stimulates the biochemical pathways activated by the receptor. When BPA impedes a receptor, it inhibits biochemical pathways activated by the receptor. For example, when BPA binds with estrogen receptors, it can enhance female traits, such as breast development. When BPA impedes androgen receptors, it can decrease male traits, such as sperm production. Studies on laboratory animals suggest that BPA may increase the risk of a variety of human diseases, including prostate and breast cancer, uro-genital abnormalities in male babies, poor sperm quality in males, early onset puberty in females, type II diabetes, obesity, and attention-deficit hyperactivity disorder.¹²

In 2008, the National Toxicology Program (NTP), an organization funded by the Department of Health and Human Services that evaluates the risks of potentially hazardous chemicals and other environmental agents, reviewed the evidence pertaining to BPA and concluded, based largely on animal data, that there is some concern that BPA could have adverse effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current exposure levels (i.e., at a dose less than the EPA's estimated safe dose). It also stated that there is minimal concern that BPA could adversely affect development of the mammary gland and lead to early puberty in females; and negligible concern that BPA could cause reproductive toxicity in adult men and women, fetal or neonatal mortality, birth defects, or reduced birth weight and growth.¹³ The NTP, National Institute of Environmental Health Sciences, and EPA continue to study BPA.^{14,15}

In 2010, the Food and Drug Administration (FDA), which had declared BPA to be safe in 2008, issued a statement saying that it concurred with the NTP's assessment of BPA, but it took no regulatory action at that time.¹⁶ The European Food Safety Authority and a panel convened by the World Health Organization also determined that there is insufficient evidence to conclude that BPA poses risks to human health. However, not all governments sided with the FDA. Canada declared BPA to be harmful to human health or the environment and banned plastic baby bottles containing BPA in 2010. That same year Denmark also banned the use of BPA in manufacturing food containers for young children.¹⁷ In 2012, the FDA also decided to ban the use of BPA in plastic baby bottles and children's cups, but the agency's decision was not based on a conclusion that BPA poses a risk to infants and children. The agency made the decision at the request of manufacturers, who had already stopped using BPA in baby bottles and children's cups, and sought an official ban to help boost consumer confidence.¹⁸ Environmental advocacy groups, such as the National Resources Defense Council, have called for extensive bans on BPA.¹⁹

BPA is not the only widely used endocrine disrupting compound with the potential to produce adverse health effects at low doses. Some others include dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), phthalate esters (chemicals used in some plastics), and brominated flame retardants (BFRs), which are used to reduce flammability of furniture, clothing and electronic equipment.^{20,21,22,23,24,25} BFRs,

which were developed as an alternative to asbestos and PCBs, were thought to be safe until evidence concerning their potential adverse health effects emerged in the last decade.²⁶

Evidence for low dose effects of endocrine disrupting compounds poses difficult questions for policymakers, because it suggests that it may not be possible to establish acceptable exposure levels for these chemicals, and the most reasonable options for risk management may be to restrict their use or ban them. However, these options create greater moral conflict than establishing acceptable exposure levels. To understand how managing the risks of endocrine disrupting compounds can involve tough choices for policymakers, it will be useful to discuss environmental risk management in more depth.

Environmental Risk Management and Value Conflict

Environmental risk management involves formulating, implementing, and enforcing policies to ensure that the risks to human health and the environment related to environmental agents, such as industrial chemicals or pollutants, are acceptable. Deciding whether a risk is acceptable is often fraught with controversy, because competing values may be at stake, including:^{27,28}

- Protecting/promoting human health
- Protecting human rights/liberties
- Promoting social justice
- Promoting social utility, including economic development
- Protecting the environment, including non-human species, habitats, ecosystems, wilderness

The first four values address human-centered concerns while the fifth deals with environmental ones.²⁹ Two or more of these five values frequently conflict in environmental risk management. For example, regulations limiting air pollutants emitted by coal burning power plants can protect human health and the environment but have adverse impacts on social utility because they may increase the costs of electricity.³⁰ Limited indoor spraying of DDT to control malaria may help protect human health and promote social utility but may threaten some species of birds and fish.³¹ Regulations that prevent the destruction of wetlands can protect the environment and promote social utility by preserving crucial ecosystem services but may interfere with property rights and entail economic costs. Deciding where to place a landfill may raise issues of social justice because people living near the landfill may face greater health risks than the rest of the population. Building a dam to increase the water supply can promote human health and economic development but may threaten the environment and conflict with the rights of those whose livelihoods or property are threatened by the dam. Though science plays a key role in these decisions by providing policymakers with information about the risks associated with environmental agents and the economic and social costs of different options for dealing with risks, decisions ultimately rest on judgments about how to adjudicate conflicts of values.^{32,33,34,35}

In thinking about the economic aspects of different actions or policies, it is important to consider not only the potential effects on industry and the larger economy, but also the impacts on health care costs for consumers, insurance companies, and governments. For example, exposure to ozone causes respiratory problems and can exacerbate allergies and asthma. Regulations that lower acceptable atmospheric ozone levels in a region may increase industry's burden and have short-term negative economic impacts but may also save health care costs by reducing treatments for respiratory problems. Since it may take many years for environmentally-induced diseases, such as cancer and emphysema, to develop, comparing long-term health care costs to short-term economic ones can be difficult. Nevertheless, health care costs should not be ignored when making environmental risk management decisions.

In deciding how to manage risks pertaining to an environmental agent, policymakers are frequently faced with three major options: 1) take no regulatory action but study the risks and inform the public; 2) establish acceptable (i.e., "safe") exposure levels; or 3) enact either a partial or complete ban on the agent's use. Options 2 and 3 are not mutually exclusive, since regulators might partially ban the use of an agent and establish acceptable exposure levels. For example, pesticides must be registered with the EPA before they can be marketed in the U.S. The EPA allows some types of pesticides to be purchased and used only by registered commercial pesticide applicators. The EPA also establishes acceptable levels of residues on food for these chemicals and requires applicators not to exceed these levels.³⁶ Policymakers may also change risk management options in response to emerging scientific evidence and evolving attitudes. For example, for many years the U.S. had no laws concerning exposure to environmental tobacco smoke (ETS). As evidence concerning the danger of ETS mounted and tolerance for smoking decreased, different jurisdictions enacted progressively stronger laws, such as bans on smoking in airplanes, buses, restaurants and bars, public buildings, parks, and even some private areas (such as automobiles occupied by children).^{37,38}

The first risk management option imposes no economic costs on industry but also does very little to protect human health or the environment. The third option maximizes environmental and human health protection but also can impose significant economic costs because it prevents companies from making, using, or commercializing an agent. The second option represents a type of moral compromise in which policymakers attempt to protect human health and the environment while minimizing economic and social costs. Though compromises may not satisfy those who occupy opposing sides of environmental health issues, they can be an effective way of bringing different stakeholders (such as environmental, public health, and industry groups) together to work toward common solutions.³⁹ But this type of compromise is feasible only when it is possible to identify acceptable exposure levels for an agent. As we explain below, acceptable exposure levels are typically determined by identifying levels at which an agent is expected to have few, if any, adverse health effects. When there is compelling evidence that compounds may have harmful effects at low doses, policymakers may need to enact regulations with greater economic or social costs in order to protect human health and the environment. These stringent regulations may be difficult to implement due to opposition from industry groups and consumers.

Studying an agent and educating the public but taking no regulatory action may be the most reasonable option when the risks are unknown and the social and economic costs required to address them are significant. For example, there is some concern that exposure to radio waves emitted by some types of cell phones may be associated with some types of brain cancer, but evidence is inconclusive at this point.⁴⁰ Regulations that ban some types of cell phones or specify acceptable designs could be difficult to enforce and would involve significant social and economic costs, because cell phone use is worldwide and companies and consumers are likely to resist regulation. Since the risks of cell phone use are uncertain, and the social and economic costs of actions designed to minimize these risks could be quite high, the best option at this point is to continue to study the risks and inform the public about the issue. Refraining from regulatory action may also be the most reasonable approach when the risks are well-established but the regulatory actions necessary to address them would unreasonably restrict rights and liberties or impose excessive social or economic costs. For example, ultraviolet radiation from exposure to sunlight is a known human carcinogen, but regulations designed to minimize exposure to sunlight, such as laws that limited outdoor activity or required people to cover their skin with protective clothing or sunscreens, would unreasonably restrict rights and liberties and impose excessive social and economic costs.⁴¹

Those who favor a precautionary approach to environmental risk management argue that regulatory action may be appropriate even when risks are unknown in order to avoid harms that are serious and irreversible. For example, some have argued for taking a precautionary approach to managing the risks of cell phone use and exposure to manufactured nanomaterials.^{42,43,44} While it may be appropriate to take regulatory action before we have conclusive scientific evidence concerning risks in some cases, these decisions should still strike a reasonable balance between environmental and health protection and competing values.⁴⁵ If a policy option threatens important moral values, then that option should not be pursued unless there are overriding reasons to do so. For example, we should not ban cell phones or require them to be redesigned until we have a better understanding of how they impact human health.

In some cases, however, there is sufficient evidence of serious risks to justify banning an agent entirely or for particular uses. This may be the most reasonable option when the risks of an agent are known and significant, scientific evidence indicates that there may be no acceptable exposure level, and the social or economic burdens of partial or complete bans of the agent are not excessive. For example, in 1970, the EPA prohibited the use of the pesticide DDT, except for some public health purposes. DDT, which persists in the environment and bioaccumulates, has well-documented adverse impacts on some species of birds and aquatic wildlife and the potential to cause human diseases.⁴⁶ In 1978, the U.S. Consumer Products Safety Commission banned lead as an ingredient in paints intended for domestic use.⁴⁷ At that time, the adverse effects of lead on neurological and cognitive development were well-established, and alternatives to using lead as an ingredient in paint were available at a reasonable cost.⁴⁸ From 1973 to 1986, the EPA gradually phased out lead as an ingredient in gasoline.⁴⁹ Limiting the use of some highly carcinogenic chemicals, such as benzene, dioxins, and vinyl chloride, may be the most reasonable way to manage these risks, since there may be no safe human exposure levels for these compounds.⁵⁰

The difficulty with enacting partial or complete bans of chemical substances is that they create significant conflicts with other values. In particular, they may generate significant social or economic costs or restrict individual rights. Therefore, regulators and judges are forced to adjudicate conflicts between important moral values when this approach is taken. In part for this reason, the U.S. ban on PCBs was not complete: PCBs that had already been manufactured remained in use.⁵¹ PCBs are banned under the Stockholm Convention on Persistent Organic Pollutants, an international agreement. Many countries have banned DDT, though some, such as the U.S., still allow it to be used for public health purposes.⁵² Total bans may not be upheld by U.S. courts, because they entail significant regulatory burdens.⁵³ For example, in 1991 a federal court invalidated the EPA's ban on asbestos (a flame retardant) on the grounds that the agency had not produced sufficient evidence to show that no other method of managing the risk, such as limiting the use of asbestos, would make the risks of asbestos acceptable.^{54,55}

Establishing Acceptable Exposure Levels

Because the first and third options run the risk of either failing to prevent hazards or creating serious moral conflicts, the second option (establishing acceptable exposure levels) represents a moral compromise that many find appealing. By identifying dose levels that appear to be safe, regulators are able to protect human health and the environment while avoiding social and economic hardships associated with partial or complete bans. While this approach will often still produce some value conflicts, these conflicts are less severe than those created by the other options when the risks of an agent are known and scientific evidence indicates that exposures to the agent below a certain level are not likely to involve significant risks. For example, the EPA has approved over 900 active ingredients used as pesticides. Companies are required to conduct tests on their products and submit data to the EPA as part of the registration process.⁵⁶ An acceptable human exposure for pesticide residue on food is established by determining the highest dose that produces no statistically significant adverse effects compared to controls in animals or the No Observed Adverse Effect Level (NOAEL). This dose is divided by an uncertainty factor of ten to account for differences between humans and animals, and then divided by another factor of ten to account for human variability, and then by a third factor of ten to provide additional protection for children. Thus, an acceptable human exposure for a pesticide would be one that produces a dose (known as the reference dose) that is 1/1000 the NOAEL in animals. Regulators use this methodology to establish acceptable exposure levels for other environmental agents, such as pollutants and industrial chemicals; however, they do not always use the third uncertainty factor, which is only required for pesticides under the Food Quality Protection Act. Sometimes the reference dose is derived from the No Observed Effect Level (NOEL) or the Lowest Observed Effect Level (LOEL).⁵⁷

Establishing acceptable exposure levels may also be the most reasonable option when the risks are known but it is practically impossible to restrict use of the agent or ban it. For example, arsenic damages the skin and circulatory system and increase the risk of cancer. Arsenic can enter drinking water from deposits in the soil or runoff from agriculture or industry. Since arsenic is present in the soil, it is nearly impossible to prevent it from entering water supplies. The EPA manages the risks of arsenic by establishing acceptable

levels in drinking water.⁵⁸ Many different types of combustion, ranging from the burning of coal in electric power plants to forest fires, produce particulate matter, which has adverse effect on the respiratory system when inhaled. Though it is not possible to prevent particulate matter from entering the atmosphere, the EPA has established particulate matter standards that states are responsible for implementing.⁵⁹

The idea that there can be acceptable exposure levels for environmental agents is based on the widely held toxicological principle that a response (such as toxicity) increases or decreases in direct relationship to the dose of an agent one receives through different routes of exposure, such as through the digestive tract, respiratory system, or skin. Below a certain threshold level of exposure, the dose is so low that the agent is assumed to be biologically inactive, so that the risks are negligible. Many chemicals do not produce cellular effects below a specific concentration. For example, nerve cells will not transmit signals unless the concentration of a neurotransmitter (such as acetylcholine) reaches a threshold concentration. Doses of chemicals below the threshold concentration level should produce virtually no toxic effects, according to this paradigm.^{60,61}

When substances do not follow this dose-response relationship, they create much greater ethical challenges for regulators. Carcinogens have been a notable exception to this dose-response orthodoxy. During the middle of the 20th century, toxicologists assumed that carcinogens are not safe at any dose. This idea was based on the assumption that all carcinogens produce adverse health effects by causing genetic damage that induces cells to grow abnormally and form tumors. Even exposure to a single molecule of an agent could (in theory) cause genetic damage and lead to cancer. This hypothesis served as the scientific basis for Delaney Amendment, which prohibits the FDA from approving any food additive that induces cancer in humans or animals.⁶² During the 1980s and 1990s toxicologists revised their thinking about the risks of carcinogens as a result of advances in the understanding of carcinogenesis. Though cancer begins with genetic damage that alters cells, other changes must also occur for tumors to grow and spread throughout the body, because organisms have mechanisms for repairing DNA, destroying cancerous cells, and suppressing tumor growth and proliferation. Some agents contribute to carcinogenesis not by causing genetic damage but by enhancing the growth and proliferation of tumors. Toxicologists now distinguish between DNA-reactive carcinogens, which cause genetic damage that results in the formation of cancerous cells, and epigenetic carcinogens, which promote cancer cell growth and proliferation. While DNA-reactive carcinogens can theoretically produce genetic damage at any exposure level, epigenetic carcinogens can be regarded as safe below a certain level of exposure because cellular effects do not occur below a certain threshold exposure level.⁶³

Endocrine disruptors also challenge the dose-response orthodoxy because they exert low dose effects. Instead of having a monotonic dose-response curve shaped like a ski slope, some endocrine disruptors (and some other chemicals) have a curve shaped like a U or upside-down U.⁶⁴ Studies have found that low but not high doses of BPA increase mammary tumor growth and metastasis in mice and adipose tissue mass in mice, and inhibit adiponectin (a hormone that increases insulin sensitivity) in human tissues.^{65,66,67} Other studies have demonstrated similar low dose effects for BPA and other endocrine

disruptors.⁶⁸ It is not known how many chemicals have nonmonotonic dose-response curves, but surveys of the toxicological literature have estimated that 12–24% of dose-response studies demonstrate nonmonotonic relationship.⁶⁹ Since hormones regulate a number of different biological systems and exert effects at low doses, one would expect that chemicals that bind with or impede hormone receptors or mimic hormones could have health impacts at low doses.⁷⁰ Whereas most carcinogens are at least expected to produce progressively smaller effects at lower dose levels, endocrine disruptors could cause much greater low-dose effects than would be expected based on their effects at higher doses. It is important to note, however, that some scientists question the evidence for nonmonotonic dose-response relationships, and they argue that there is no need to radically rethink environmental risk management to deal with low dose effects of chemicals.⁷¹ Others argue that low dose exposures to some chemicals sometimes have beneficial effects on human health by inducing adaptive responses, but this hypothesis is controversial.^{72,73,74,75}

In sum, adverse low dose effects of environmental agents can create difficult choices for policymakers by limiting risk management options. When an agent has no significant low dose effects, regulators can allow the agent to be introduced into commerce or the environment, provided that procedures and rules are in place to keep exposures below an acceptable level. This option allows society to maximize the benefits from the use of the agent while minimizing risks to human health or the environment, and represents a compromise between competing values. For example, pesticides can play an important role in controlling insects that feed on crops or carry diseases, or in killing weeds that compete with crops for nutrients. Prudent use of pesticides can help to improve crop yields.⁷⁶ If an agent produces adverse effects at low doses, regulators may face difficult choices between permitting or not permitting use of agent, since the option of allowing use at a certain level of exposure may not provide adequate protection for human health or the environment. These choices often involve conflicts between protecting human health and the environment on the one hand, and interfering with human rights and liberties or imposing social and economic costs on the other. Stakeholders on opposing sides of these issues (such as environmental and industry groups) are likely to advocate for contradictory policy options, making it difficult to achieve workable compromises.⁷⁷

Returning to the BPA Controversy

The difficult ethical issues that we have highlighted can be illustrated by returning to the BPA case. As we have already seen, some governments have decided not to establish acceptable levels of BPA exposure through baby bottles or cups, but have decided, instead, to ban these uses of BPA. In making the decision to ban a particular use of BPA, regulators must compare the benefits, risks, and costs of allowing the use versus the benefits, risks, and costs of not allowing the use. They must also consider whether there are safe and effective alternatives to BPA, since a chemical used instead of BPA might also poses risks to human health or the environment. In deciding whether to ban the use of BPA in manufacturing baby bottles or children's cups, regulators must ascertain whether there are alternative methods of manufacturing these items that are more safe and effective than using BPA. Bisphenol S, for example, may not be a safe alternative to BPA because this chemical also acts as an endocrine disrupter and has a nonmonotonic dose-response curve.⁷⁸ However,

polypropylene appears to be a safe and effective alternative to BPA in plastic containers, and companies have already begun using this chemical even without regulatory pressure.⁷⁹

While the decision to ban the use of BPA in baby bottles and children's cups has not posed intractable dilemmas for regulators, due to the availability of safe and effective alternatives, more challenging questions could arise concerning the use of BPA in food can linings. Metallic cans were developed in the 19th century as a cheaper alternative to food storage in glass. Some form of protective lining is necessary in metallic cans to prevent corrosion and food spoilage. Food manufacturers have found that alternative chemicals are more expensive than BPA and that BPA can still be detected in food even when alternatives are used. In 2009, Vital Choice began making tuna containers without using BPA, but tests conducted by the Consumers Union still found traces of BPA in the tuna. Company representatives are not sure how BPA entered the tuna, but they speculate that it could have leached into the tuna from gloves, cutting boards, or other items used in food preparation. Because BPA exposure is widespread, the tuna could also have acquired BPA from the environment.⁸⁰

If it is not practical to make canned food completely BPA-free, then perhaps the most reasonable risk management option would be to establish standards for acceptable levels of BPA in food. But, as we have seen, BPA's adverse low dose effects challenge the feasibility of this option. In principle, policymakers could still establish exposure levels that they considered acceptable, but those levels would not achieve the typical goal of ensuring the protection of human health; rather, they would be the result of an effort to weigh human health protection against the social impacts of limiting the use of BPA. Thus, policymakers will continue to face difficult decisions about how best to manage the risks of BPA, i.e., whether to limit its use through some type of ban, establish acceptable exposure levels, or pursue a combination of both options. Regulations that limit the use of BPA may help to promote human health but have a negative impact on commerce, industry, and society. For example, if using alternatives to BPA in food can linings significantly increases the costs of canned food, this would have adverse impacts on the food industry as well as consumers. Increases in the costs of canned food could make food less affordable and thereby increase hunger, and would have disproportionate impacts on economically disadvantaged people, since they tend to spend a higher portion of their income on food. It is also important to consider the potential long-term costs to individuals, insurers, and society from the adverse health effects of BPA. These costs are difficult to determine at present, because BPA's impacts on health are not well-understood currently, but they should be factored into the assessment of BPA's social and economic impacts. These and other possible consequences would need to be considered in developing BPA risk management policies.

Conclusion

Managing the risks of endocrine disrupting compounds poses difficult ethical questions for policymakers because these chemicals may threaten human health or the environment at low doses. As a result, the moral compromise of establishing acceptable exposure levels may be difficult to achieve, and policymakers may need to adjudicate among conflicting values and opposing stakeholders when deciding whether and how to restrict the use of these chemicals. The failure to reach a compromise position can exacerbate moral and political conflict

concerning the management of chemicals and lead to protracted litigation and resistance to implementation. To help achieve workable compromises policymakers and companies should continue to look for creative ways to manage the risks of these chemicals. For example, they should continue to explore whether there are conditions and dose levels (e.g., lower than 5 mg per kg of body weight per day) that are not likely to have significant adverse effects. Governments should also look for ways to incentivize industry to develop and employ safer alternatives to endocrine disrupting chemicals and other worrisome classes of chemicals.⁸¹

Acknowledgments

We are grateful to Bruce Androphy and Bill Schrader for helpful comments. This article is the work product of an employee or group of employees of the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH). However, the statements, opinions or conclusions contained therein do not necessarily represent the statements, opinions or conclusions of NIEHS, NIH, or the United States government.

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