



**Are  
"Low Dose"  
Health Effects  
of Chemicals  
Real?**



# Are “Low Dose” Health Effects of Chemicals Real?

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Based on a report by Michael A. Kamrin, Ph.D., of Michigan State University,  
which will be published in the *International Journal of Toxicology*

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# Executive Summary

- It has been claimed that low doses of hormonally active substances in the environment may cause health problems that do not occur in response to higher doses. This allegation is highly controversial.
- Between 2000 and 2002, expert panels in the United States and Europe critically evaluated the evidence available at that time for low dose effects of bisphenol A, the most studied compound. The panels concluded that a low dose effect on reproduction or development had not been conclusively established and noted that the findings of different studies had not been consistent.
- Substantial additional research has been completed since the expert panels evaluated the low dose hypothesis. However, the validity of the newer research on low dose effects is as uncertain as the validity of the earlier studies. The general conclusions reached in earlier evaluations remain valid. The studies that have been alleged to support the low dose hypothesis cannot be validly extrapolated to the human situation; the effects observed in these studies are inconsistent and not necessarily harmful; and the doses at which the studies have been performed are higher than the doses to which people are customarily exposed.
- Careful assessment of all of the available data, including both animal and human evidence, indicates that the low dose hypothesis remains unproven. There is no compelling evidence that people are being put at risk by current levels of exposure to bisphenol A or other substances alleged to be “endocrine disruptors.”

Concerns were raised during the late 1990s about the possibility that hormonally active substances in the environment may cause health problems when present in low doses. It has been alleged that these so-called “low dose” effects cannot be detected using traditional toxicology studies, which involve the administration of high doses of test substances to experimental animals. This idea, called the *low dose hypothesis*, is highly controversial. In this report, the American Council on Science and Health evaluates the scientific evidence pertaining to the low dose hypothesis, including recent studies that were completed after expert panels evaluated the evidence on this topic several years ago. The principal source for this report is a technical review by Michael A. Kamrin, Ph.D., of Michigan State University, which will be published in the *International Journal of Toxicology*.

## Introduction

During the early 1990s, it was alleged that reproductive and developmental problems in wildlife might be linked to hormonally active synthetic compounds in the environment. Concerns were raised that similar effects might occur in people. However, formal scientific studies did not show any link between environmental agents and the suspected adverse effects.

By the late 1990s, the nature of the concerns had shifted. Claims were made that the hormonally active compounds were indeed causing harmful effects at low doses but that these effects had not been detected in earlier research because they occur *only* at low doses, not at high ones, and therefore would not be observed in conventional high dose toxicology studies. It

was also asserted that the low doses at which effects occur in experimental animals are similar to the doses to which people are commonly exposed, indicating that the human population is at risk.

Much of the research on alleged low dose effects has focused on bisphenol A, a substance used in the manufacture of many consumer products, including some types of plastic bottles. Very small amounts of bisphenol A may migrate into foods and beverages from plastic containers, thereby exposing people to low doses of this substance. Critics of bisphenol A claim that it is an “endocrine disruptor,” meaning that low doses might interfere with the normal functioning of body hormones, with resulting adverse effects on reproduction and development.



## Effects at High and Low Doses

It has usually been assumed that adverse effects of substances are more likely to occur at high doses than at low doses. A high enough dose of anything can be harmful, but lower doses of the same substance may not be. In fact, low doses may be safe, beneficial, or even essential for life. Vitamins, for example, are essential for life in small amounts but some can cause serious harm when consumed in excessive amounts. Similarly, many pharmaceuticals that have beneficial effects at therapeutic doses have harmful effects if consumed in larger doses.

What the low dose hypothesis proposes is that in some instances, low doses of a substance may have adverse effects that do not occur at higher doses. The idea that a substance may have an effect at low doses that differs from those at higher doses is not new. There is scientific evidence that a wide variety of substances, both natural and synthetic, can have such effects; the term *hormesis* has been used to describe this phenomenon. These low dose effects may be beneficial, adverse, or neutral. The controversy over low dose effects of bisphenol A and similar substances does not focus on whether it is possible for such effects to exist — scientists know that they can. Instead, it focuses on whether the scientific evidence currently available indicates that these particular compounds actually have such effects and, if they do, whether these effects have any relevance for human health.

## Older Evaluations

Between 2000 and 2002, expert panels in the United States and Europe critically evaluated the evidence available at that time for low dose effects of bisphenol A, the most studied compound. Both concluded that a low dose effect on reproduction or development had not been conclusively established. The reports commented on the lack of reproducibility of some of the findings. It was difficult to interpret the data because the results of different studies did not agree.

## Newer Evidence

A significant number of new studies of low dose effects have been completed since the scientific panels mentioned above met and reached their conclusions. It has been claimed that this new research provides convincing evidence of a variety of low dose effects. To evaluate this claim, the results of the research studies must be examined to see whether they are scientifically valid. Several important criteria must be considered.

### Criteria for Assessing the Experimental Evidence

*Are the data reproducible?*

One basic principle of science is that findings must be reproducible from one study to another in order to be considered valid. In studies that test substances for adverse effects, reproducibility means that the same effects are seen in multiple studies and that the response to a particular dose is the same from study to study. The same substance, administered to the same kind of animals at the same dose, should produce the same result. If this does not happen, then it's likely that any effects seen are due to some other factor — one that varied from study to study, such as some aspect of the animals' environment — rather than to the test substance itself.

*Are the data consistent?*

Do the results fit a pattern? When testing is performed in different species or under different conditions, do the findings fit a common explanation? The results obtained in different species or under different conditions need not be identical, but the patterns should make sense. Mice may be consistently more sensitive to a substance than rats are, for example. Effects might only occur in older animals, not younger ones. If an effect is real, patterns such as these should emerge from the data.

*Were the studies conducted properly?*

Scientific data are only as good as the studies that produced them. For a study to be valid, it must be designed correctly. For example, it should include control subjects — untreated animals of the same species and strain as the test animals, raised in the same place, with the same diet and environment. The study should be performed under appropriate experimental conditions. More than one dose should be tested so that responses to different doses can be compared, and studies should be performed for a long enough time that researchers can determine whether any changes observed are temporary or permanent.

*Were the results interpreted correctly?*

To interpret results properly, one must remember that change and harm are two different things. The mere fact that a detectable change occurred in the body does not necessarily mean that any kind of harm occurred. For example, if you swallow a vitamin tablet containing the B vitamin riboflavin, a yellow-green fluorescence will appear in your urine shortly afterward (the vitamin is fluorescent, and excess amounts are quickly excreted from the body). This is completely harmless. It is an example of a change that is not indicative of an adverse effect. Similarly, changes occurring in an experimental animal's body in a low dose study — such as an increase or decrease in the weight of a body organ or a change in the synthesis of a body chemical — are not necessarily indicative of harm. Further research would be needed to assess whether the change is harmful, beneficial, or neutral.

*Are the findings relevant to the human situation?*

Most of the studies investigating possible low dose effects have been conducted either in experimental animals, usually rats or mice, or in cultured cells. However, the real concern is about effects in the human population. Therefore, it is important to ask questions such as the following: Are the conditions under which

the experiment was performed relevant to the human situation? Is the route of exposure relevant to human routes of exposure? Are the doses administered similar to those to which people are exposed? Is the fate of the test substance in the human body the same as that in the animal species or culture system used, and are the actions of the substance similar in the two species?

## **Assessing the Validity of the Low Dose Studies**

When evaluated using the criteria discussed above, the validity of the newer research on low dose effects turns out to be as uncertain as the validity of the earlier studies. The general conclusions reached in earlier evaluations remain valid. Despite the completion of additional research, it is still true that the low dose studies of bisphenol A and similar substances lack consistency and reproducibility. Moreover, there is still little support for the claim that the results of these studies indicate that people are at risk from low dose exposures.

As was true in earlier studies, recent findings have varied from one study to another. For example, prenatal exposure to bisphenol A was associated with increased prostate weight in male offspring in one study but not others. Similarly, the observation that adult male animals exposed to bisphenol A had lower sperm numbers has not been seen consistently in different studies. Similar disparities have been seen in studies of effects on female animals, such as changes in the weight of the uterus. Thus, while effects have been detected in some experimental animals under some conditions, it appears that there is no clear pattern of reproductive and developmental changes. And it is important to note that in some studies, no effects of any kind have been detected.

Responses to different doses have also been inconsistent. In some studies, lower doses have produced effects while higher doses have not; in others, the opposite situation has occurred. In

still other studies, only one dose was administered, making the assessment of the dose-response relationship impossible.

One possible reason why researchers have encountered so much inconsistency in their study of low dose effects is that the endpoints they are measuring may be very variable and easily affected by a variety of factors. For example, it has been suggested that the presence of substances that have estrogenic effects in an animal's feed may influence the results of low dose studies, thereby accounting for some of the observed variability. It is unclear whether this is true, though, and if it does prove to be true, it might further complicate interpretation of study findings. Like experimental animals, people eat diets that contain varying amounts of estrogenic substances. Does this mean that studies of animals fed estrogen-free diets cannot be extrapolated to people who consume diets that include significant amounts of estrogens? Or vice versa?

Since only a few low dose studies have been conducted in human populations (these studies will be discussed in the section below on "Human Evidence"), scientists' understanding of low dose effects in people must be based primarily on extrapolations from other types of studies, combined with an understanding of the actual exposures of human population groups. The key question to be answered is "Are the exposures being investigated 'environmentally relevant,' meaning that they are comparable to the ways in which humans would be exposed?"

The researchers who have performed low dose studies have often argued that the results of their experiments are indeed "environmentally relevant." However, in many instances, this claim does not appear to be valid. In the case of bisphenol A, for example, estimates indicate that human exposure is somewhere in the range of 0.002 to 0.4 micrograms per kilogram of body weight per day, but experiments using doses as high as 400 micrograms per kilogram of body weight per day (1000 times higher than the upper limit of the human exposure range) have been claimed to be environmentally relevant.

Almost all of the reported low dose effects of bisphenol A have occurred at doses well above the estimated human exposure level.

The way in which experimental animals are exposed to a substance should also be environmentally relevant if the results are to be applicable to people. Some bisphenol A studies in whole animals were performed using methods of exposure, such as injection, that are not applicable to the human situation, where exposure would occur through food or water. Nevertheless, the researchers who conducted these studies have claimed that they are environmentally relevant.

Those low dose studies that were conducted using cultured cells rather than whole animals should not be considered environmentally relevant. Extrapolation to the human situation from cell culture studies is inappropriate. In cell culture, the substance being tested is not exposed to the normal processes that occur in a living animal or person, and the cells are not in their normal environment. It is especially inappropriate to extrapolate concentrations of chemicals used in cell culture studies to animal or human doses. Cell culture studies are useful primarily to help understand the way in which a substance exerts its effects, rather than in directly predicting what those effects will be.

Another important issue in the evaluation of the low dose studies involves the types of effects measured in some of these studies — what researchers call the *endpoints* of the studies. Since the focus of interest is hazards to the human population, the endpoints should consist of some type of harm or at least be markers for an adverse effect. Many of the endpoints that have been used in low dose studies are biochemical or structural in nature rather than focusing on function. Therefore, it is unclear whether they are indicative of harm. For example, some studies have examined DNA synthesis in reproductive cells or prostate weight in animals exposed to a substance while in the womb rather than fertility or reproductive success. A change in one of these structural or biochemical end-

points does not necessarily imply that the ability to reproduce has been impaired even in the animals being tested, let alone in humans. In fact, some of the endpoints observed in low dose studies might even be indicative of beneficial health effects. Some of the effects seen in low dose studies of synthetic chemicals are the same as those produced by naturally occurring *phytoestrogens* (estrogen-like substances from plants), such as resveratrol, which is found in grapes and blueberries, and genistein, which is found in soybeans. The overall effect of these phytoestrogens in the food supply is believed to be beneficial to health.

## Human Evidence

Only a very few studies reporting possible low dose effects in human populations have been performed.

There has been much publicity surrounding a recent study suggesting that maternal exposure to phthalates (compounds mainly used as plasticizers) affects the distance between the genitals and the anus in male babies. However, care must be taken in assessing the significance of this single study. There have been other cases in which highly publicized epidemiological studies suggested that an environmental agent was associated with an effect but subsequent larger and more careful studies failed to confirm this association. Moreover, the endpoint of this study is poorly understood; scientists do not know how much the distance between the genitals and the anus varies naturally or what the implications of this measurement might be.

Two other reports claiming evidence of reproductive effects in humans include one describing a correlation between bisphenol A levels and ovarian dysfunction and another describing an association between bisphenol A levels and miscarriage. In both studies, there is reason to suspect that the observed differences in bisphenol A levels might be a *result* of hormonal differences between the groups of women rather than a *cause* of them. In fact, the scientists who con-

ducted the ovarian dysfunction study suggested this as the likely explanation for their findings. It is also a plausible explanation for the findings of the miscarriage study, which compared women with a history of repeated miscarriages with women who had never been pregnant. If hormonal changes during pregnancy influence the body's metabolism of bisphenol A, a study could easily show a difference between women who had been pregnant (as the women with repeated miscarriages obviously had been) and those who had never been pregnant, even if the substance is unrelated to miscarriage.

## Conclusions

In summary, careful assessment of all of the available data, including both animal and human evidence, indicates that the low dose hypothesis remains just that — a hypothesis. The available data do not establish that low dose effects of bisphenol A and similar substances are real or that exposure to these substances at low doses produces adverse health effects in people. The studies that have been alleged to support the low dose hypothesis cannot be validly extrapolated to the human situation; the effects observed in these studies are inconsistent and not necessarily harmful; and the doses at which the studies have been performed are higher than the doses to which people are customarily exposed. There is no compelling evidence that people are being put at risk by current levels of exposure to bisphenol A or other substances alleged to be “endocrine disruptors.”



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