New report finds EPA's controlled human exposure studies of air pollution are warranted

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The U.S. Environmental Protection Agency (EPA) carries out experiments in which volunteer participants agree to be intentionally exposed by inhalation to specific pollutants at restricted concentrations over short periods to obtain important information about the effects of outdoor air pollution on human health. A new report by the National Academies of Sciences, Engineering, and Medicine finds these studies are warranted and recommends that they continue under two conditions: when they provide additional knowledge that informs policy decisions and regulation of pollutants that cannot be obtained by other means, and when it is reasonably predictable that the risks for study participants will not exceed biomarker or physiologic responses that are of short duration and reversible.

In controlled human inhalation exposure (CHIE) studies, participants are exposed to one or several common air pollutants usually for a few hours at concentrations that are not expected to produce adverse responses. The goal is to observe temporary and reversible responses without causing clinical effects. The studies are designed to minimize the effects of extraneous factors and focus on the relationship between the experimental exposure conditions and the biologic response being measured, for example, a temporary change in lung function. These experiments are done in order to understand pathways of toxicity by which air-pollutant exposures might lead to illness or premature death to sensitive individuals in the general population.

Results from CHIE studies are used to inform the periodic review of National Ambient Air Quality Standards (NAAQS) for common pollutants, such as ozone and particulate matter (PM), and advise other policy decisions. The NAAQS process has broad health importance because it regulates the outdoor air concentrations of those pollutants. The committee that conducted the study and wrote the report examined the contributions of CHIE experiments to the scientific information used for the reviews of NAAQS for ozone and PM. Ozone and PM CHIE studies have enabled investigators to separate the effects of exposure to such individual pollutants from effects associated with exposures to ambient complex mixtures. They have provided unique information on short-term exposure-response relationships that cannot be obtained from animal inhalation studies or epidemiologic studies of people engaged in their normal daily activities.

To assess the level of safety provided by study protocols and the likelihood of participants experiencing any serious health effects with long-term consequences, the committee reviewed eight recent CHIE studies. The committee concluded that the societal benefits of CHIE studies are greater than the risks posed to the participants in the eight studies considered, which are unlikely to be large enough to be of concern. EPA applies a broad set of health-evaluation criteria when selecting participants to determine that there is no reason to believe that their participation in the study will lead to an adverse health response. The health status of subjects is monitored shortly before, during, and immediately after the exposure studies and usually again about 24 hours later.

The biologic responses of the participants in the past studies, as anticipated by the study protocol, dissipated once the exposure to air pollutants stopped and did not result in any serious effects with long-term consequences. Out of the 845 intentional pollutant exposures conducted at EPA's study facility from Jan. 2009 to Oct. 2016, one

participant developed an unexpected episode of irregular heart beat during an experimental PM exposure. The individual reverted to a normal heart rate spontaneously, within two hours after the exposure, and was hospitalized overnight for observation. This one hospitalization, which corresponds to 0.1 percent of the experimental pollutant exposures, illustrates that despite substantial efforts to screen potential participants, there is some level of risk in these studies. The committee said it is not possible to definitively say that there was no risk to the subjects in these studies.

"While communicating with potential participants, it's particularly important to appropriately characterize the risks," said Robert Hiatt, professor of epidemiology and biostatistics at University of California, San Francisco, and chair of the committee. "EPA needs to make every effort to ensure that these descriptions are accurate, scientifically grounded, and comprehensible to people."

The report calls for improvements in the way consent information is communicated with potential participants. For example, some of the current consent documents used by EPA are limited by their use of complicated and technical language. The committee recommended that EPA use plain language in presenting risks, provide information on the occurrence of serious adverse events associated with previous CHIE studies, and explain how those events were resolved.

While not all possible risks can be listed in a consent disclosure process, the Academies' report says study consent forms should list all health risks for which there is some credible evidence that harm might occur. Risks likely to be perceived as important by participants should be included even though there is no credible evidence to suggest they are reasonably foreseeable. For example, participation in a PM CHIE study would add little risk of cancer or heart diseases because the extent of exposure during the study is very small compared with the total PM

exposures that many people experience in the U.S over many years. In addition, any increase in chronic disease risk resulting from PM exposures in the studies would be vanishingly small, the report says. According to the committee, allowing people to judge risks for themselves and determine if they are willing to assume those risks is essential in respecting the autonomy of participants.

Going forward, the report recommends EPA regularly review and update its risk-profile information on groups that show sensitivity to air-pollutant exposures to inform decisions on who should be included in CHIE studies and who should be excluded. The report also recommends that the EPA convene an external scientific advisory committee of experts on a regular basis to ensure that the most important CHIE study topics are selected in order to maximize the rigor and impact of each study.

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