

Although the focus of the cessation lag discussion in the SAB review was on reducing levels of arsenic in drinking water, much of their consideration of this issue has more general applications beyond just the arsenic issue at hand. In particular, SAB noted the following:

- The same model should be used to estimate the time pattern of exposure and response as is used to estimate the potency of the carcinogen.
- If possible, information about the mechanism by which cancer occurs should be used in estimating the cessation lag (noting that late-stage mechanisms in cancer formation imply a shorter cessation lag than early stage mechanisms).
- If specific data are not available for characterizing the cessation lag, an upper bound for benefits can be provided based on the assumption of immediately attaining steady-state results.
- In the absence of specific cessation lag data, other models should be considered to examine the influence of the lag.

Following the release of the SAB report on arsenic, EPA initiated an effort to explore approaches to including the cessation lag in modeling risk reduction and calculating benefits for the arsenic regulation. EPA recognized, however, that the concept of cessation lag is not only applicable to arsenic but to other drinking water contaminants having a cancer end-point as well.

In response to the SAB cessation lag recommendations, EPA has:

- Conducted a study using data on lung cancer risk reductions following cessation of smoking that resulted in the January 2003 report *Arsenic in Drinking Water: Cessation Lag Model* (USEPA 2003s).
- Conducted an expert scientific peer review of that draft report.
- Initiated development of general criteria for incorporating cessation lag modeling in benefits analyses for other drinking water regulations.

In the effort to develop a cessation lag model specific to DBPs, EPA reviewed the available epidemiological literature for information relating to the timing of exposure and response, but could not identify any studies that were adequate, alone or in combination, to support a specific cessation lag model for DBPs in drinking water. Thus, in keeping with the SAB recommendation to consider other models in the absence of specific cessation lag information, EPA explored the use of information on other carcinogens that could be used as a

indicator to characterize the influence of cessation lag in calculating benefits. The carcinogen for which the most extensive database was available for characterizing cessation lag was for cigarette smoking. EPA examined several extensive epidemiological studies on the comparison of the risks of adverse health effects, including lung cancer, for smokers and former smokers. EPA selected the Hrubek and McLaughlin (1997) study as the most appropriate study for development of a statistical model of disease response to smoking cessation. This was a comprehensive study involving a 26-year follow-up of almost 300,000 U.S. male military veterans. More detail about this study and how it is applied to estimate the cessation lag can be found in Chapter 5 of the EA (USEPA 2003i) and the cessation lag document (USEPA 2003s).

The smoking cessation lag data imply that the majority of the potential steady state cases avoided occur within the first several years, but with diminishing incremental increases in later years. For example, the cessation lag model indicates that approximately 40 percent of the steady-state cases avoided are achieved by the end of the second year, with 70 percent achieved by the end of the fifth year, and approximately 80 percent by the tenth year. By the twentieth year, 90 percent of the steady state cases are avoided.

EPA recognizes that there are several factors that contribute to the uncertainty in the application of the specific cessation lag model used in the estimation of the benefits of the proposed Stage 2 regulation. A key factor to consider in assessing this impact is the likely mode of action of DBPs in eliciting bladder cancer versus the mode of action of tobacco smoke in producing lung cancer, and in particular whether they behave as initiators or promoters of the carcinogenic process. As discussed in the SAB report and the EPA Cessation Lag report (USEPA 2001e, USEPA 2003s), carcinogens that act solely or primarily as initiators would tend to show a longer cessation lag (lower rate of risk reduction following reductions in exposure) than carcinogens that act solely or primarily as promoters. The available information on tobacco smoke and lung cancer suggests that it involves a mixture of both initiators and promoters, and therefore the cessation lag derived from smoking data is expected to reflect the combined influence of these divergent mechanisms. There are no data available on the mechanism of action for DBPs and bladder cancer; indeed the specific carcinogenic agent(s) present in

disinfected water responsible for the observed effect have not been identified. The use of the tobacco smoke cessation lag model reflecting a mixture of initiators and promoters would be expected to attenuate a possible bias in either direction if the DBPs responsible for bladder cancer are acting predominately as either initiators or promoters.

Another factor to consider is that the cessation lag model used is based upon exposure to tobacco smoke where lung cancer is the end-point but is being applied to exposure to disinfection by-products where the end-point is bladder cancer. Of concern here is that there is a more direct correlation between inhalation and the site of cancer for smoking than there is for ingestion and inhalation of drinking water and the sites of cancer for DBP exposure. Unfortunately, EPA does not have data on which to develop a cessation lag model using data specific to how changes in DBP exposures affect the risks of developing bladder cancer.

Another divergence, and perhaps the most important, between the smoking model and the DBP application is that the smoking model is based on complete cessation of exposure, whereas in the case of DBP exposure is only being reduced. In some water systems the reduction is only 10 percent, whereas in others it may be as high as 60 percent, with an average of approximately 30%. This moderate reduction in exposure may prevent full DNA repair, which some scientists interpret as the basis for the short cessation lag associated with smoking.

Currently, smoking is the only contaminant for which enough data exist to estimate a cessation lag. In the absence of a reliable cessation lag model based specifically on DBPs and bladder cancer, EPA used the cessation lag model based on smoking to provide a means of estimating the rate at which bladder cancer risk in the exposed population falls from the pre-Stage 2 levels to the post-Stage 2 levels. However, this model is derived from data involving notable differences from DBPs in drinking water, including different cancer sites (lung versus bladder), different exposure pathways (inhalation versus a combination of ingestion, inhalation and dermal), different risk levels, and, perhaps most importantly, complete cessation for smoking versus small exposure decreases for DBPs. For these reasons, the extent to which the smoking / lung cancer model is directly transferable to DBP / bladder cancer is uncertain. It is not possible to know, however, whether and to what degree the tobacco smoke

based on the observed latency would greatly underestimate the actual benefits."