# Data considerations for regulation of water contaminants

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## Abstract

There are several pieces of legislation based on human health assessment that set the framework for U.S. EPA's regulation of water contaminants, such as bromate. The Safe Drinking Water Act, for example, specifies that the best available science be used in support of regulation of drinking water contaminants, and highlights that regulations must provide protection to sensitive human populations. Recent EPA guidance, including the 2005 *Cancer Guidelines*, emphasize analyzing data, and using defaults only in the absence of adequate data. This represents a major shift from the former practice of invoking default methodologies or values *unless* it was judged that there were sufficient data to depart from them. The Guidelines further present a framework for assessing data in order to determine if a mode of action (MOA) can be established, based on a modification of the Bradford–Hill criteria for causality. A similar approach is used by the International Programme on Chemical Safety (IPCS). To illustrate the application of the framework for evaluating animal tumors, three case studies are considered here. In the first example (chloroform carcinogenicity), sufficient data exist to identify the MOA in animals, and the data are used to illustrate the evaluation of the plausibility of the animal MOA in humans, taking into account toxicokinetics and toxicodynamics. In this case, the MOA was judged to be relevant to humans, and was used to determine the approach for the cancer quantitation. In the second example (naphthalene inhalation carcinogenicity), the key question is whether the weight of evidence (WOE) is sufficient to establish the MOA in animals. Atrazine-induced mammary tumors form the final example, illustrating the reasoning used to determine that the tumor MOA in animals was not considered relevant to humans; atrazine is therefore considered not likely to be a human carcinogen.
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*Keywords:* Mode of action; Chloroform; Naphthalene; Atrazine; Weight-of-evidence

## 1. Legal framework for a research agenda

In formulating a research agenda for bromate it is useful to consider the ways in which data can be used to support regulation; conversely one can consider the data requirements of risk assessments on which regulations may be based. There are several pieces of legislation based on human health assessment that set the framework for U.S. EPA's regulation of water contaminants. These include the Clean Water Act (CWA) of 1977, the Food Quality Protection Act (FQPA) of 1996, and the Safe Drinking Water Act (SDWA), last amended in 1996. The CWA gives EPA authority to set effluent standards on an industry basis (technology-based); these regulations may consider human health and the benefits of protecting human health. EPA is also given authority to set national criteria (and in some cases State standards) for all contaminants in surface waters; these criteria can be based on human health or protection of aquatic

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organisms. Regulation of contaminants in drinking water is addressed by the SDWA, which is discussed in the next paragraph. The FQPA is an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act that highlights risks of pesticides to children. FQPA requires a revised safety standard for all pesticides used in food; namely, that there be reasonable certainty of no harm. As water is considered a food, the mandates of this law apply to drinking water contaminants. One of the applications of FQPA is that in the absence of data specific to childhood risk, non-linear quantitative assessments may incorporate an additional 10-fold safety factor. When data relevant to childhood risk are available, those data are incorporated in the assessment. In general, the EPA Office of Water's interpretation of this requirement is that it applies specifically to pesticides, or perhaps to other chemicals designed to be toxic or have biological activity (such as antibiotics).

The SDWA amendments covered many areas of the law, including some changes that are germane to data requirements in support of regulations. SDWA 1996, for example, specifies that the best available science be used in support of regulation of drinking water contaminants. EPA includes in the definition of best science that data, and assessments based on those data, be peer reviewed as well as available to the public. SDWA 1996 highlights that regulations must provide protection to sensitive human populations. These populations include not only sensitive life stages (such as children, fetuses and the elderly) but also groups such as those with genetic pre-disposition to certain health effects, immunocompromised people and so on. Another SDWA 1996 consideration is the reinforced obligation to review existing National Primary Drinking Water Regulations on a 6-year cycle.

Bromate is one of several disinfectant by-products regulated and monitored under the Stage One Disinfectant By-products Rule (DBP) issued in 1998. A regulatory limit in water, or Maximum Contaminant Level (MCL) of 10 μg/L was established in this rule. According to SDWA, MCLs are to be set as close as feasible to the Maximum Contaminant Level Goal. For bromate the MCLG was set at zero, which was standard practice for a contaminant considered to be a probable human carcinogen. The Stage Two Disinfectant By-products Rule (signed 15 December 2005) maintains the MCL of 10 μg/L for bromate. The Stage Two Disinfectant By-products Rule and the underlying assessments (for bromate and other DBP) will be reviewed under the next applicable 6-year cycle.

SDWA 1996 made a fundamental change in the way EPA sets regulations for drinking water contaminants.

Instead of following lists of contaminants set out in earlier versions of SDWA, the 1996 amendments required EPA to establish Contaminant Candidate Lists (to be revised periodically as specified in the law) and to make five regulatory determinations every 5 years from the items on the list. In order to regulate water contaminants, EPA must now answer affirmatively in three areas:

1. Does the contaminant adversely affect public health?
2. Is the contaminant known or likely to occur in Public Water Systems with a frequency and at levels posing a threat to public health?
3. Will regulation of the contaminant present a meaningful opportunity for health risk reduction?

These questions, as well as the necessity of demonstrating benefits of the rule commensurate with its projected costs, help determine the broad outlines of the research agenda for drinking water contaminants.

The research agenda is also informed by evolution of risk assessment philosophies and methodologies. Recent discussions of EPA's *modus operandi* can be found in several current documents: *An Examination of EPA Risk Assessment Principles and Practices* (known as the *Staff Paper*) (U.S. EPA, 2004); the *Guidelines for Carcinogen Risk Assessment* (*Cancer Guidelines*) (U.S. EPA, 2005a); the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposures to Carcinogens* (*Supplemental Guidance*) (U.S. EPA, 2005b). The remainder of this paper will draw from and expand on those sources.

## 2. Risk management levels (MCLs) incorporate risk assessment (MCLGSs)

SDWA 1996 still relies on the calculation of a Maximum Contaminant Level Goal (MCLG), based on assessment of human health risk. The MCLG is a non-enforceable public health goal, usually expressed as an amount of contaminant in μg/L of water. Historically some established choices were used. For "carcinogens", defined as those agents classified as Group A, Known Human Carcinogen or Group B, Probable Human Carcinogen under the 1986 *Cancer Guidelines*, the MCLG was set at zero. MCLGs for so-called non-carcinogens were based on a Reference Dose (RfD) calculated from a NOAEL or LOAEL (no observed adverse effect level or lowest observed adverse effect level) and using standard uncertainty factors. Defaults for exposure were used: 2 L water/day for a 70 kg adult and 1 L of water/day for a 10 kg child. For "C carcinogens", those categorized as
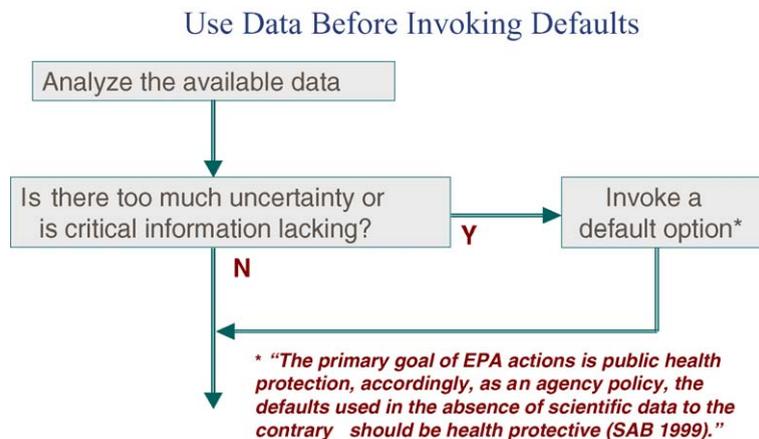
## Use Data Before Invoking Defaults



Fig. 1. Emphasis on analyzing data and using defaults only if those data are lacking.

Possible Human Carcinogen under the 1986 Guidelines, the MCLG was based on an RfD to which an additional safety factor (NOT uncertainty factor) of 10 was applied. (An uncertainty factor characterizes an area of uncertainty or variability and can be replaced by data; a safety factor is a risk management entity.)

These practices have largely changed or are in the process of changing. The *2005 Cancer Guidelines* and the *Staff Paper* articulate two major shifts in risk assessment as done by U.S. EPA. The first has to do with use of defaults and assumptions. The former practice was to invoke default methodologies or values unless it was judged that there were sufficient data to depart from them. The 2005 Cancer Guidelines makes a complete shift in that they emphasize analyzing data and using defaults only if those data are lacking. This is illustrated in Fig. 1. Related to this shift is the increased consideration of reliance on mode of action in determining weight of evidence for all types of hazard characterization, as well as in choosing methods for low-dose extrapolation. Thus, research programs that elucidate mode of action provide the critical data to inform all decisions regarding risk.

## 3. Mode of action

### 3.1. How is mode of action determined?

The *2005 Cancer Guidelines* provide a definition of mode of action:

> The term "*mode of action*" is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A "*key event*" is an empirically observable

precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element. Mode of action is contrasted with "*mechanism of action*," which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action. The toxicokinetic processes that lead to formation or distribution of the active agent to the target tissue are considered in estimating dose but are not part of the mode of action as the term is used here. There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.

The Guidelines further present a framework for assessing data in order to determine if a mode of action can be established. This framework is a modification of the Bradford–Hill criteria for causality. A similar approach is used by the International Programme on Chemical Safety (IPCS) (Sonich-Mullin et al., 2001). Under the *Cancer Guidelines* framework, each mode of action is analyzed separately, noting that multiple modes of action may contribute to the development of a given tumor type, and that a single chemical may cause tumors in different tissues by different modes of action. Note that this framework can be used to judge MOA for any sort of health-related endpoint; it is not restricted to carcinogenicity.

The framework includes these components:

1. *Description of the Hypothesized MOA*. This begins with a *summary* for each likely MOA and includes the *identification of key events*. Key events are measurable events that are critical steps in the induction of tumors by the hypothesized mode of action.

2. *Discussion of the Experimental Support for the Hypothesized MOA*. This is the component that parallels the Hill criteria. The following criteria are considered:
   a. *Strength*, *consistency*, *and specificity of association* of tumor response with key events—discussion of the weight of evidence linking the key events, precursor lesions, and tumors.
   b. *Dose response concordance*
   c. *Temporal relationship*—if an event is causally linked to tumorigenesis, it will precede tumor appearance.
   d. *Biological plausibility and coherence*—consideration of whether the postulated mode of action is consistent with current understanding of carcinogenesis in general (biological plausibility) and the specific chemical (coherence).
3. *Consideration of the Possibility of Other Modes of Action*. This should include the possibility that different MOA operate in different dose ranges or routes of exposure.
4. *Conclusions about the Hypothesized MOA*. Three questions in particular need to be addressed:
   a. *Is the hypothesized MOA sufficiently supported in the test animals?*
   b. *Is the hypothesized MOA relevant to humans?*
   c. *Which populations or lifestages can be particularly susceptible to the hypothesized MOA?*

Recent work under the auspices of the International Life Sciences Institute (ILSI) and the IPCS has expanded this framework to include specific consideration of the human relevance of the MOA (Seed et al., 2005; IPCS, 2005), providing a structure for rigorous evaluation of all of the data relevant to both the animal and human MOA. Under this framework, the following issues are considered:

1. Is the weight of evidence sufficient to establish a MOA in animals?
2. Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans?
3. Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between experimental animals and humans?
4. Conclusion: statement of confidence, analysis, and implications.

### 3.2. Case studies on MOA

To illustrate the application of the framework for evaluating animal tumors, three case studies are considered here. In the first example (chloroform carcinogenicity), sufficient data exist to identify the MOA in animals, and the data are used to illustrate the evaluation of the plausibility of the animal MOA in humans, taking into account toxicokinetics and toxicodynamics. In this case, the MOA was judged to be relevant to humans, and was used to determine the approach for the cancer quantitation. In the second example (naphthalene inhalation carcinogenicity), the key question is whether the weight of evidence (WOE) is sufficient to establish the MOA in animals. Atrazine-induced mammary tumors form the final example, illustrating the reasoning used to evaluate whether the tumor MOA in animals is plausible in humans. Atrazine illustrates an example wherein the tumor MOA in animals was not considered relevant to humans; therefore, atrazine is considered not likely to be a human carcinogen.

### 3.2.1. Chloroform

Chloroform carcinogenicity is well-studied, and the MOA for chloroform has been exhaustively assessed and reviewed. The available data and the resulting cancer assessment, are reviewed in U.S. EPA (2001). In brief, chloroform has been shown to result in liver and kidney tumors in rodent bioassays. The postulated MOA to explain these tumor responses involves oxidative metabolism of chloroform by cytochrome CYP2E1 as the rate-limiting step. Metabolism by this pathway produces cytotoxic metabolites in the target organ, in particular the highly reactive chemical phosgene. The cytotoxic metabolites injure and kill cells, and this damage is followed by regenerative cell proliferation. Tumor development can result if the cytotoxicity/regenerative proliferation is sustained. Thus, the three key steps are oxidative metabolism, cytotoxicity and cell death, and regenerative cell proliferation. This MOA is summarized in Fig. 2, and lines of evidence for it are discussed briefly below.

Chloroform has been tested in a large number of genetic toxicology assays, and the weight of evidence indicates a lack of mutagenicity in vitro. Those few positive responses were observed at cytotoxic levels or in assays known to have a high incidence of "false positives", that is, in tests which respond to chemicals known not to be carcinogenic. The weight of evidence that chloroform is not genotoxic is reinforced by observation of non-positive responses in sensitive in vivo tests. For example, there was no increase in mutation frequency in
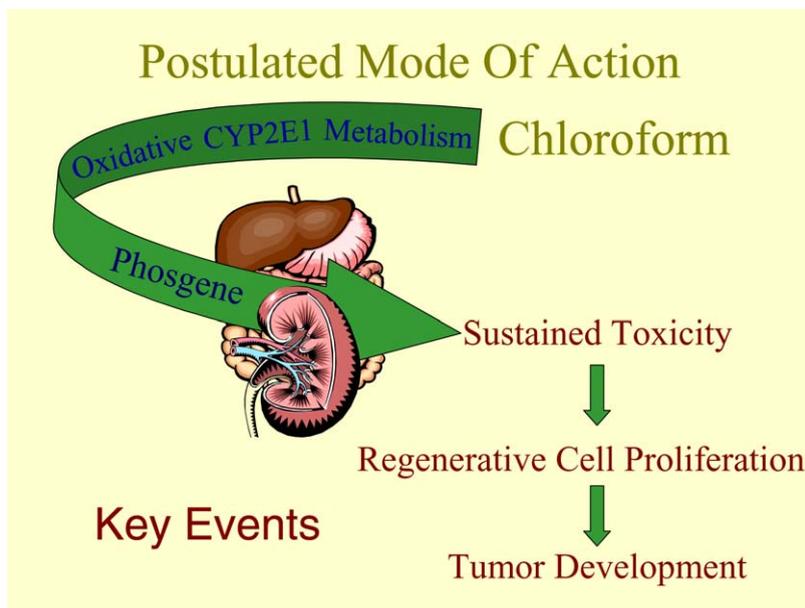
Fig. 2. Postulated mode of action for chloroform.

indicator genes in male mice exposed to levels of chloroform associated with tumor formation. While chloroform may be metabolized via three pathways, there are several lines of evidence that in vivo, the predominant pathway is the CYP2E1-mediated oxidative pathway, producing phosgene. While reductive metabolism might lead to mutagenic metabolites, it appears that the reductive pathway would be operative only under conditions of high chloroform exposure in animals which have been treated specifically to induce the enzymes of that pathway.

There is a strong relationship between doses that cause sustained toxicity and cell proliferation and those that cause tumors. Evaluation across a number of combinations of species–sex–target organ–dose conditions has shown that cytotoxicity and sustained cell proliferation is a necessary, but not sufficient, condition for the development of tumors. In other words, tumors occur only under conditions (species–sex–target organ–dose combinations) that produce cytotoxicity, but not all conditions that produce chloroform-related cytotoxicity also result in tumors. In all cases where tumors occur, they are preceded by toxicity and cell proliferation. Overall, the postulated MOA for chloroform is well-supported, and alternative MOAs are not well-supported. Human relevance is presumed for the MOA as all three key steps are known to occur in humans. It was further determined that the MOA applies to children, but children are not expected to have increased susceptibility; it appears that CYP2E1 is minimally expressed in fetal and neonatal tissue, and the developing organism is not particularly

sensitive to cytotoxic agents at low levels. The data are consistent with a non-linear dose–response, with the risk management approach based on protection against sustained toxicity and regenerative cell proliferation.

### 3.2.2. Naphthalene

A recent inhalation bioassay with naphthalene (NTP, 2000) found "*clear evidence of carcinogenic activity*" of naphthalene in male and female F344/N rats based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose. In a related study in mice (NTP, 1992) there was *some evidence of carcinogenic activity* in female B6C3F$_1$ mice, based on increased incidences of pulmonary alveolar/bronchiolar adenomas, and *no evidence of carcinogenic activity* of naphthalene in male B6C3F$_1$ mice. A number of potential modes of action may be considered for the observed tumors.

The overall weight of evidence indicates that genotoxic activity of naphthalene is demonstrated primarily in assays that measure chromosomal effects, rather than gene mutations (reviewed by NTP, 2000 and U.S. EPA, 1998). Naphthalene was negative for gene mutations in *Salmonella typhimurium* and in metabolically competent human lymphoblastoid MCL-5 cells at the *tk* and *hprt* loci. It was positive for chromosome aberrations in CHO cells in the presence of exogenous metabolic activation, as well as in micronucleus assays in MCL-5 cells and in salamanders, and in *Drosophila* recombination tests, but not in some micronucleus assays in

mice. NTP (2000) also noted that the results indicate that the genotoxic effects of naphthalene require, or are enhanced by, cytochrome P450 enzymes, but that the metabolic activation in mutagenicity test systems would not be expected to include the CYP2F2 enzyme. This enzyme is selectively expressed in lung and olfactory mucosal cells and plays a key role in the bioactivation of naphthalene in the nose. Some scientists have noted the absence of liver tumors following exposure to naphthalene as evidence for the absence of a genotoxic mode of action, presuming that the putative genotoxic metabolite would be formed in the liver. This consideration is important, but needs to be considered in light of the observed tissue-specific differences in naphthalene metabolism, with higher metabolic capacity in the rodent respiratory tract than in the liver. To address this issue, it would be useful to conduct genotoxicity studies with naphthalene using homogenates prepared from the target tissue (or even the target tissue region), to insure that the active metabolites are formed.

Results for the proposed naphthalene metabolite 1,2-naphthoquinone are mixed, but some positive results have been obtained in gene mutation assays, and a genotoxic MOA is plausible for quinones. The naphthalene metabolites 1-naphthol and 2-naphthol were negative for gene mutations in *S. typhimurium*, and 1-naphthol was negative in several other assays, including gene mutations in mouse L5178Y cells, and micronuclei in mouse and rat bone marrow cells.

Cytotoxicity has been hypothesized as the mode of naphthalene tumorigenesis, in light of the observed (albeit imperfect) correlation between the non-cancer and cancer lesions. In order to establish cytotoxicity as the MOA, one would need to identify the key event (e.g., a specified metabolite causes death of cells in certain target regions, followed by regenerative cell proliferation). The key toxic metabolite of naphthalene has not been identified. While it may be feasible in general to identify a narrow group of metabolites as part of the identification of the mode of action, the species-specific differences in metabolism mean that identification of the specific metabolite is important for naphthalene in order to evaluate the human relevance of the tumors. There are a number of consistencies between the tumor and presumed precursor lesion for cytotoxicity. For example, the cytotoxicity MOA appears to meet the tests of dose–response and biological plausibility. However, there are also a number of inconsistencies. For example, mice and rats both develop nasal respiratory epithelial lesions, but only male rats get tumors; mice have no nasal tumors. Similarly, there are regional and sex-related inconsistencies in the nasal tumors in rats. Atrophy, hyaline degeneration,

and hyperplasia were observed in the respiratory epithelium of both male and female rats, but only males had respiratory epithelial tumors. Conversely, only female rats had olfactory epithelium tumors, although both sexes had similar non-cancer lesions in this tissue. Thus, the available data on the cytotoxicity MOA do not appear to meet the test of consistency. No data were located to evaluate the test of temporality, in the absence of intermediate sacrifices. Based on the overall data, particularly the lack of consistency between occurrence of cytotoxicity and tumors, the cytotoxicity MOA does not appear to meet all of the criteria of the framework.

Other hypothesized MOAs include mitogenesis due to direct stimulation of cell division or indirect DNA damage due to reactive oxygen species. Endocrine-related modes of action have also been hypothesized to explain the sex-related differences in the observed tumor response. However, insufficient data are available to support these modes of action at the current time, due to insufficient data on early events and the steps needed to cause tumors.

Overall, there are a number of data gaps that preclude the identification of the tumor MOA for naphthalene. The metabolite responsible for the observed tumors has not been identified. The data supporting each potential MOA needs to be evaluated separately for each tumor target. While the overall data indicate that the genotoxic potential of naphthalene is mostly negative, a genotoxic MOA for the naphthalene metabolite 1,2-naphthoquinone is plausible. EPA's cancer guidelines specify that determination of MOA for the purpose of identifying the approach for low-dose extrapolation generally requires the affirmative identification of the applicable MOA. The 2005 *Cancer Guidelines* state that if no MOA can be established "and when scientifically plausible based on the available data" (U.S. EPA, 2005a), then linear extrapolation is used as the default approach.

### 3.2.3. Atrazine

Atrazine is a triazine pesticide that induces mammary gland tumors in female SD rats, but not in F344 rats, CD mice, or male SD rats. A substantial database has been developed by a number of authors over the past 10 years that shows that these tumors are produced via an endocrine-mediated cascade of events culminating in prolonged exposure to endogenous hormones. This in turn leads to the increased incidence of mammary tumors observed in the SD rats. Data do not support other modes of action such as direct estrogenic activity, and the weight of evidence for genotoxicity is clearly negative. The genetic toxicology database for atrazine shows consistent negative responses in bacterial tests,

and inconsistent positive responses across other phylogenetic lines (which are typically weak, found at high doses, or cannot be reproduced). This is the case both for atrazine as well as for known metabolites.

These data have been extensively reviewed and are summarized in several EPA documents (U.S. EPA, 2002a,b), which delineate the lines of evidence supporting each of these steps. The following sequence of events has been identified for atrazine-induced carcinogenesis. (1) Atrazine directly or indirectly affects the hypothalamus, leading to decreased secretion of hypothalamic norepinephrine. (2) Decreased norepinephrine results in decreased release of gonadotropin releasing hormone (GnRH), and decreased levels of GnRH have an effect on the pituitary gland (studies show that atrazine does not have a direct effect on the pituitary gland to induce tumors). (3) The pituitary gland, under influence of the decreased GnRH, attenuates the release of luteinizing hormone (LH) (studies show that atrazine affects LH cycling). (4) Disruption of normal LH cycling results in increased exposure to both endogenous estrogen and prolactin; the normal functioning of the ovaries is affected. (5) These altered exposures to reproductive hormones enhance the growth of mammary neoplasms (ovariectomized rats exposed to atrazine do not develop tumors). Fig. 3 and the preceding description give the barest outline of this elegant mode of action and the data supporting it.

The scientific community, including the U.S. EPA Scientific Advisory Panel (SAP) agree that this MOA is the means whereby atrazine causes tumors in female Sprague-Dawley rats. EPA proposed that human relevance should be assumed for both the cancer and noncancer effects of atrazine, based on identification of prolonged estrogen exposure as a risk factor in human breast cancer, and general similarity between human and other mammalian endocrine feed back mechanisms. The SAP, however, concluded that the mode of action is not supportive for human cancer concern. The Panel noted that there are certain similarities in the control of the hypothalamic-pituitary-ovarian axis between humans and rats but that there are important differences in the details of the control mechanism. It was strongly emphasized that the effects of age on reproductive and endocrine function are much different between rats and humans. SAP noted that there are also differences in the aging process among rat strains; it appears that the mechanism of atrazine action in the Sprague-Dawley rat is unique to that strain and that a similar process is not operable in Long-Evans or F-344 rats. There are no data from humans suggesting that atrazine interferes with hypothalamic-pituitary-ovarian function. It was noted that if atrazine did reduce LH and induce hypothalamic amenorrhea in exposed women, this condition is associated with reduced estrogen levels and thus would not promote the development of mammary tumors. The SAP concluded "*there are considerable differences between hypothalamic-pituitary-ovarian function in rats and humans, and the effects of aging on the function of the axis also is quite dissimilar. Therefore, it is unlikely that the mechanism by which atrazine induces mammary tumors in female SD rats could be opera-*
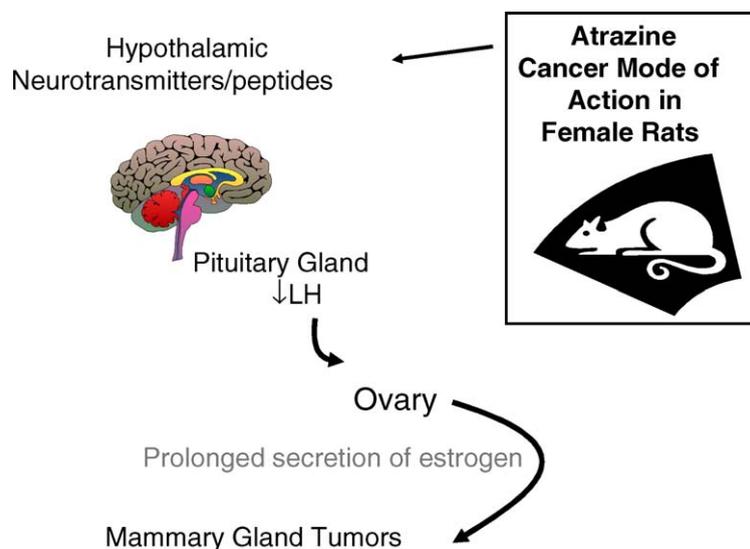


Fig. 3. Proposed mode of action for atrazine's tumorigenicity.

*tional in humans*." All, however, agreed that the known endocrine effects of atrazine raise concern for possible developmental and/or reproductive effects of exposure during critical life stages.

## 4. Conclusions: what does the risk assessor do with the MOA?

The above case studies focused on hazard identification, an obvious use of MOA information. These case studies illustrate the types of data that may be needed to address the questions in the frameworks for evaluating MOA and evaluating the human relevance of the MOA in experimental animals. This information can then be used in designing studies to clarify the MOA for bromate tumorigenicity. Knowledge of MOA will help in categorizing the weight of evidence that an agent causes cancer or some other effect in humans. The MOA may elucidate special sensitivity (or lack of susceptibility) of certain lifestages or human populations. MOA can inform the risk assessor as to conditions of exposure likely to be associated with an effect (e.g., long term versus short term, episodic or chronic, route of exposure, high dose or low). MOA also leads one to choices regarding low-dose extrapolation.

Much of the discussion around MOA and dose–response assessment has been of choices between linear and non-linear low-dose extrapolation. The *Staff Paper* (U.S. EPA, 2004), as well as recent risk assessment publications, point out that there is actually a choice among non-linear approaches. These can include the following: a probabilistic estimation of risk at an exposure level; a benchmark dose approach to establishing a point of departure, from which one could derive an RfD or calculate a margin of exposure; a traditional RfD based on N/LOAEL. In the spirit of the 2005 *Cancer Guidelines*, it is also appropriate to choose a data-based approach over use of standard uncertainty factors when the data support this. A research strategy, based on thoughtful consideration of the uses of data, can help ensure that sufficient

information will be at hand to construct assessments of risk that are reflective of reality.

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