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Utilizing the Six Sigma Framework to Radically Change EPA's Integrated Risk Information System (IRIS)

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Abstract

In 1985, EPA created the Integrated Risk Information System (IRIS) as a database to provide Agency consensus positions on the human health effects of chemicals found in the environment. This database is important because it provides consistency across EPA when setting policy and regulations, provides a central place for the States and local health departments to go when unregulated chemicals are detected in air and water, functions as guidance to industry scientists, and is a central place for international organizations to go to regarding the health effects of environmental chemicals. This process worked effectively until the mid-1990s when EPA expanded the development process for IRIS assessments, with the process continuing to expand since that time. In 2009, the Government Accountability Office (GAO) added IRIS to the list of government operations it identified as "high risk" based on problems with productivity, credibility, and transparency. In 2019, the GAO concluded that EPA had addressed some of its identified issues, including transparency, but had not made progress in productivity; i.e. producing chemical assessments. This is what demands a fundamental process change: any process that delivers so little output is a failure. This paper uses some of the elements of the Six Sigma Framework to evaluate work processes at IRIS and suggests radical changes to improve its performance.

Introduction

What is an Integrated Risk Information System (IRIS) Assessment?

The goal of IRIS is to produce health values that provide the basis for policy, regulations, and guidance used by individual EPA offices, States, local health agencies, other federal agencies, and international health organizations. The health values that are calculated on IRIS are levels of individual chemicals that are calculated to not harm people after breathing the chemical in the air, or drinking it in the water, over a lifetime [1]. The central value of IRIS is that it provides a consistent database of health values that are used by all the individual offices across EPA. Without this, each EPA office would use their own diffuse individualized data sources to calculate different data values for the same chemical. This is not only confusing within the Agency but is also confusing outside the Agency, because States, local health officials, and industry would not have an official EPA position to rely on. This would very likely lead to errors and defects. Therefore, having a consistent database that everyone, both within and outside of EPA can draw upon, is a core value of IRIS. IRIS only deals with the health effects of chemicals after long-term exposure; there are other programs that deal with the short-term effects of chemicals after emergency response situations such as spills or accidental releases. For example, under the Emergency Planning and Community Right to Know Act (EPCRA), facilities must immediately report accidental releases of hazardous substances in quantities greater than their "Reportable Quantities" (set by EPA) to state and local officials [2]. IRIS assessments are currently carried out by EPA's Office of Research and Development (ORD) [1]. IRIS assessments include the first two steps of a full risk assessment:

- Hazard Identification: identifies credible health hazards associated with exposure to a chemical.
- Dose-Response Assessment: characterizes the quantitative relationship between exposure to a chemical and each credible health hazard. These quantitative relationships are then used to derive toxicity values [1].

In plain English , "Hazard Identification" consists of a review of the scientific literature to determine what are the major health effects after a person is exposed to a chemical. "Dose-Response Assessment" uses the results of the literature review to identify a relevant study or studies that will be used as the basis for the health values and calculates health values based on the study or studies. See Figure 1 for a summary of the health values available on IRIS and Appendix 1 for further details on the health values.

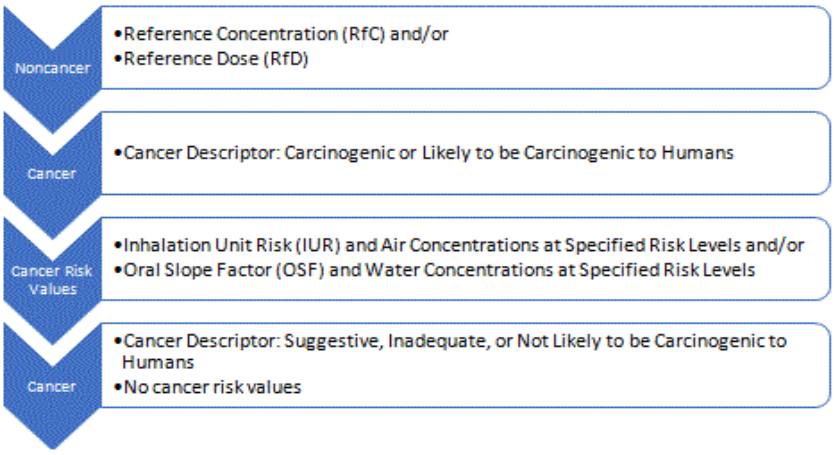

Figure 1: Risk Values on IRIS

How IRIS Assessments are Used

When IRIS was initially established, it functioned primarily as a database to present an Agency-wide position on chemicals in the environment. Before 1995, two senior EPA risk assessment workgroups met monthly to evaluate health values from EPA offices and to place their own final health values on IRIS. In 1995, this process was changed; the Agency workgroups were disbanded (see Table 1 for a summary of the changes to IRIS over the years) and the Agency-wide focus no longer appeared to be the primary focus of IRIS. EPA's ORD continued to conduct its own risk assessments which it posted on IRIS but they were no longer used uniformly throughout EPA [3]. The main reason for this was the slow pace of IRIS; EPA offices decided that waiting 10 years or more for an assessment was not acceptable, so they derived their own health values or used health values derived by individual States or other Agencies. In the 1980s and 1990s, health values listed on IRIS were considered to be EPA official health values, providing consistency across EPA when EPA offices set their own policy and regulations. This is an important goal that needs to be retained. For this to happen, the output of IRIS needs to be greatly increased from its current level.

It is important to understand that IRIS assessments are not based on any legal or statutory authority, but are often used by EPA offices as the basis for regulations that are mandated by environmental legislation. Figure 2 shows the EPA offices that often use the health values on IRIS as the basis for setting regulations. EPA offices use the IRIS assessments as inputs to the full risk assessment process. As previously noted, IRIS assessments only include the first two steps of a full risk assessment; the last two steps of a risk assessment are carried out by EPA offices and others for regulatory or other purposes.

These steps are:

- Exposure Assessment: assessment of the human exposure to the chemical under different exposure scenarios.
- Risk Characterization: combining exposure assessment with the hazard and toxicity values from IRIS to characterize potential public health risks [1].

In plain English, exposure assessment examines how many people are exposed to a chemical and how they are exposed; i.e., through air, water, or other ways. Risk characterization consists of combining how many people are exposed to the chemical with the health values calculated on IRIS to determine how large a health risk exists for the general population.

One of the most important uses of IRIS is at the State and local levels. State and local health agencies use the toxicity values on IRIS for clean-up levels at hazardous waste sites or "safe" levels of contaminants in air and water. In the absence of federal regulations, IRIS values may become de facto regulations when used by States or others to determine clean-up levels at hazardous waste sites or "acceptable" levels in air and water. For example, if a State finds an unregulated chemical in drinking water, they may compare the concentration level to a health value, such as the RfD. If the concentration level is below the RfD, the State may say it does not present a risk, if it is above the RfD, the State may say it presents a risk and will order treatment of the drinking water to remove the chemical. If there is no RfD or other health value for the chemical, the State may determine that if any level of the chemical is detected, the drinking water must be treated, even if the chemical does not present an actual risk. Alternatively, a States may decide that if there is no health value, the chemical does not pose a risk, and not treat the drinking water. Either ends of the spectrum are suboptimal and lead to a lack of uniformity across the country in dealing with environmental chemicals, underscoring why the States need an IRIS process that results in more chemicals being assessed and completed. To restate, IRIS is important because:

- It provides consistency across EPA when setting policy and/or regulations. For example, without IRIS, the Office and Air and Radiation and the Office of Water would use different health values when setting regulations for the same chemical. This results in confusion and inconsistent policies across the Agency, causing distrust among the regulated community.
- It provides a central place for the States and local health departments to go to when they encounter a chemical that is not regulated in air or water. It also provides a level of consistency when the same chemical is detected in different States across the country.
- It functions as guidance to industry scientists who use the health values to evaluate chemicals used in processes in industry.
- It is a central place for international health organizations to go to regarding guidance from the U.S. government on environmental chemicals.

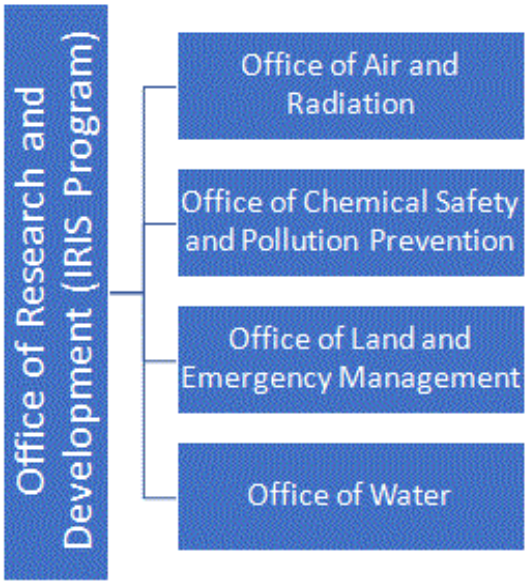

Figure 2: EPA Offices Using IRIS

Table 1. History of IRIS (1)

Year	Action
1985	EPA establishes Agency-wide workgroups on health effects of chemicals found in the environment. IRIS created as an internal database to provide these consensus health effect values .
1987	The first IRIS summaries added to internal EPA database.
1988	IRIS database made publicly available via email and National Library of Medicine's TOXNET system.
1996	EPA implements a new process for developing IRIS assessments. Process consists of a nomination process, development of a Toxicological Review document, independent external peer review, public comment on the draft document, consensus Agency review, and posting the final assessment on IRIS.
1997	IRIS database uploaded to the internet.
2004	EPA revises process to include Office of Management and Budget (OMB)-led interagency review before external peer review and before posting final IRIS assessments.
2008	EPA revises process to include nominations for IRIS assessments by other Federal agencies and an interagency meeting on these nominations, identification of mission critical chemicals by other federal agencies, development of draft assessment without health values followed by Agency, interagency, and public review and comment, a public listening session on the draft assessment without health values, opportunity for research to close data gaps, a public listening session on the full draft assessment, review of the revised assessment and disposition of comments by external peer reviewers.
2009	EPA revises process to include a streamlined review schedule so that most assessments would be posted on IRIS within two years of the start date.

2011	The National Research Council (NRC) reviews the draft IRIS assessment for formaldehyde and suggests implementation of systematic review methods.
2012	EPA holds a public stakeholder meeting to discuss a range of topics related to IRIS, including communication, transparency, and stakeholder engagement.
2013	EPA introduces a new document structure for IRIS Toxicological Review Documents reflecting adoption of systematic review methods.
2013	EPA holds a workshop to examine the "state of the science" of systematic review methodology.
2014	The NRC reviews the IRIS assessment process and concludes that the IRIS program had moved steadily forward in planning for and implementing changes in the assessment process.
2014	EPA establishes "Chemical Assessment Advisory Committee" (CAAC) to provide expert advice on IRIS Toxicological Reviews.
2015	EPA holds a workshop on "advancing systematic review" for chemical assessments.
2015	EPA releases multi-year agenda for the IRIS program, which is a reprioritization of the 2012 IRIS agenda.
2018	NRC holds a workshop to review systematic review and progress made by IRIS since the NRC's 2014 report and issues a report based on information at the workshop.
2018	EPA prioritizes IRIS assessments to meet the highest needs of EPA offices, continuing assessments for 13 chemicals, discontinuing assessments for 8 chemicals and suspending assessments for 9 chemicals.

Why Reform is needed

Low productivity

As of November, 2018, IRIS contained information on 510 chemicals [1]. This is a very small number of the total chemicals used in the U.S. today. The Toxic Substances Control Act (TSCA) requires EPA to compile and publish a list of each chemical substance that is manufactured or processed, including imports, in the U.S. for uses under TSCA. This inventory is called the TSCA Inventory and currently contains more than 86,000 chemicals [4]. This means that EPA has only addressed on IRIS 0.00006% of the chemicals in the TSCA Inventory. Even though IRIS assessments are probably not appropriate for all 86,000 chemicals (i.e. some may not be released into the environment or may dissipate after short-term exposure), it is clear that EPA has not even addressed a small percentage of the total chemicals with IRIS assessments. Of the 510 chemicals on IRIS, approximately 75% of these assessments were completed in the 1980's and 90's and the remaining were completed from 2000-2019 [1]. The process begun in 1996 of a nomination process and extensive peer review, continued in 2008 with 12 new steps added to the process, and continuing through today with new methodologies being proposed, has extended by years the process of getting anything done. As Figure 3 shows, the IRIS process has ballooned from a simple one-step process to a lengthy, multi-step process, leaving little doubt as to why so few assessments have been completed since the 1990s. See Appendix 1 for a summary of the IRIS process for arsenic and formaldehyde, two chemicals for which the IRIS assessments have been in development, but not finished, for more than 30 years and counting.

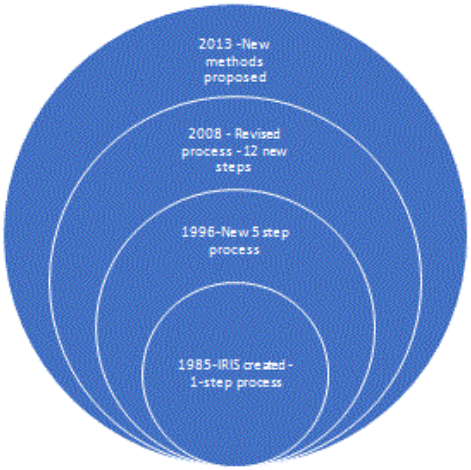

Figure 3: Key Changes to the IRIS Program

Transparency

In 2011, the National Research Council (NRC) reviewed the draft IRIS assessment on formaldehyde and concluded that the assessment was not prepared in a consistent fashion and did not contain sufficient documentation on methods used to identify and evaluate studies in risk assessment. The NRC recommended that EPA use a systematic review process of the scientific literature to operate in a more transparent way on all the IRIS assessments [5]. Systematic review is a methodology that was initially established for use in clinical medicine for evaluating data in making recommendations for health care. In the past, this methodology was used primarily for human clinical trials and consisted of the evaluation of small sets of data of similar design [6]. Over the past 10 years, this approach has been used to review

environmental health issues. The Office of Health Assessment and Translation, within the National Toxicology Program (NTP), has adopted a framework for systematic review for reaching hazard identification conclusions for environmental health issues [6]. They have developed a seven-step framework for synthesizing findings from studies in literature-based assessments as follows:

1. Problem formulation and protocol development
2. Search for and select studies for inclusion
3. Extract data from studies
4. Assess quality of individual studies
5. Rate confidence in the body of evidence
6. Translate confidence ratings into evidence of health effects
7. Integrate evidence to develop hazard identification conclusions.

Systematic review provides a greater level of transparency and clarity compared to other literature review methods because every step of the process is clearly laid out and documented. There is no question as to why studies were included or excluded from the assessment because the protocol is clear and verifiable.

Systematic review appears to work well for small assessments looking at well-defined issues, such as have been done by the NTP. NTP has prepared a number of reports using systematic review to review environmental health issues. For example, they prepared a systematic review of the long-term neurological effects following acute exposure to sarin gas [7]. The literature and screening process identified 34 human studies and 51 animal studies that met the inclusion criteria, and only considered studies on neurological effects observed after 24 hours of exposure [7].

However, the use of systematic review does not work well for large assessments examining issues that are not well defined – such as those in the IRIS assessments. The reason is that systematic review greatly increases the length of time needed to complete the assessments. For example, the systematic review protocol calls for two reviewers to independently screen all references at the title and abstract level and resolve differences by agreement through discussion. In addition, assessing the quality of the individual studies is a very lengthy process, with all references being independently assessed for quality by two independent reviewers who resolve their differences through discussion [6]. For IRIS assessments that typically contain thousands of references, this process is unwieldy and not workable. EPA is currently preparing IRIS assessments for arsenic, chromium, and PCBs using systematic review. Currently, the IRIS schedule for 2019 has listed arsenic, chromium, and PCBs as being in the draft development stage, with an external peer review draft for arsenic projected for 2021 and chromium and PCBs for 2022 [8]. It is not surprising that EPA is projecting a two-year period for developing a draft document for arsenic and a three-year period for developing a draft document for chromium and PCBs. There will then be at least several years before the draft documents become final, translating into completion of documents in approximately 2023. Also, these are not new documents. As discussed in Appendix 1, the arsenic IRIS assessment has been under development for 30 years, and chromium and PCBs have also been under development for long time periods. Therefore, for IRIS assessments, the use of systematic review will only increase the problem of the slow pace of IRIS.

GAO Reports on IRIS

Three GAO reports on IRIS have concluded that the major area needing improvement is productivity; i.e. production of the assessments in a timely manner.

GAO (2008):

- EPA's actions since 2000 to address its backlog of 70 ongoing assessments and to respond to new OMB requirements "have not enabled EPA to routinely complete credible IRIS assessments or decrease its backlog."
- In 2006 and 2007, EPA sent 32 assessments to OMB for the first of three required external reviews and EPA only finalized four assessments in this period. In addition, as of December 2007, most of the 70 ongoing assessments had been in progress for over 5 years. "This low level of productivity jeopardizes the viability of the EPA database."
- Conclusion: "EPA needs to re-evaluate its draft proposed changes to the IRIS assessment process in light of the issues raised in this report and ensure that any revised process clearly defines and documents a streamlined IRIS assessment process" [9].

GAO (2009):

- In 2009, GAO added IRIS to the list of government operations it identified as "high-risk." Historically, high risk areas were designated because of their greater susceptibility to fraud, waste, abuse, and mismanagement, but the high-risk designation has also been used to "draw attention to areas associated with broad-based transformations needed to achieve greater economy, efficiency, effectiveness, accountability, and sustainability of selected key government programs and operations."
- As of December 2007, 69% percent of ongoing assessments had been in progress for more than five years, and 17% had been in progress for more than 9 years. In addition, in 2003, data indicated that more than half of the existing assessments (540 in 2003) were outdated.
- Conclusion: EPA had not incorporated its suggestions on how to streamline and increase the transparency of its IRIS assessments and the process changes begun in 2008 only increased its productivity and credibility concerns [10].

GAO (2019):

- EPA had addressed many process challenges in the IRIS program, including the length of time it takes to develop chemical assessments and to increase transparency, but it had not made progress in producing chemical assessments.
- Conclusion: Use of project management principles and specialized software, tailoring assessments to Program and Regional office's needs, and streamlining the peer review process will make the IRIS process more efficient, and its use of systematic

Process Improvement – Six Sigma Methodology

There are a number of process improvement methodologies that have been developed for the purpose of increasing productivity and scaling businesses [12]. These methodologies lay out a process for evaluating and improving processes. This paper will use tools from the Six Sigma Methodology, which is widely used in the manufacturing industry today, to evaluate the work process at EPA's IRIS. Six Sigma defines the following steps for improving existing processes:

- Define the opportunity for improvement (project goal).
- Measure the performance of your existing process.
- Analyze the process to find any defects and their root causes.
- Improve the process by addressing the root causes you found [12].

Opportunity for Improvement

The first step is defining the opportunity for improvement, i.e. defining the project goal. The goal in this paper is to assess the performance of EPA's IRIS program since it began in 1985 and suggest concrete changes to improve its performance.

Measure the Performance of the Existing Process and Analyze the Process to Find Defects

The second step is to measure the performance of the existing processes and the third step is to analyze the process to find any defects and their root causes. Each of these two steps will be examined separately for the sub processes in the current EPA work process for IRIS (see Figure 4):

- Identify chemicals
- Hazard Identification
- Dose-response assessment
- Review process
- Post on IRIS.

Figure 4: Work Process for IRIS

Identify Chemicals

Measure Performance

The first sub process is to identify chemicals for IRIS assessments. The current process consists of EPA publishing a Federal Register Notice that informs the public that they may nominate chemicals for IRIS assessments within a 60-day period. In addition, EPA has a separate process by which other Federal Agencies may nominate chemicals for IRIS assessments, followed by an interagency meeting on these nominations [1].

Analyze Process to Find Defects

There is no coordination between EPA and the States, industry scientists, and local health departments on the chemicals needing IRIS assessments.

Hazard Identification

Measure Performance

As previously discussed, hazard identification consists of a review of the literature to determine the health effects from exposure to the chemical. EPA's current process consists of a very lengthy hazard identification process which culminates in the preparation of an IRIS Toxicological Review Document. To understand the additional burden and length of time that makes this process unworkable, the following is a listing of the chapters that are in a typical IRIS Toxicological Review Document:

Chemical and Physical Properties Relevant to Assessments

- Chemical and Physical Information: The chemical formula, molecular weight, vapor pressure, solubility, and melting point of the chemical.

• Sources of Exposure, Fate and Transport: Information on production and uses of the chemical and how it is transported in the environment.

Toxicokinetics Relevant to Assessments

• Absorption: How the chemical is absorbed in the human body, i.e. through breathing, ingesting, or absorbing it through the skin.
• Distribution: The major organs where the chemical is distributed within the body.
• Metabolism: How and where the chemical is broken down within the body.
• Elimination: How the chemical is eliminated from the body, i.e. through the breath, urine or feces.

Hazard Identification

• Studies in Humans: Epidemiology studies (studies in humans) that investigate health effects from exposure to the chemical in the workplace or the environment.
• Sub chronic and Chronic Studies and Cancer Bioassays in Animals: Studies in laboratory animals (usually rats and mice) that range from several months to several years and study either non cancer or cancer effects.
• Reproductive/Developmental Studies: Epidemiology studies or studies in laboratory animals examining the effects of the chemical on reproduction and the developing fetus.
• Other Duration or Endpoint-Specific Studies: Short-term studies (less than several months long) and/or studies on other endpoints that were not included in the above sections, such as on the brain or muscles.
• Mechanistic Data: Studies that examine how the chemical causes its effects in the body; these are usually studies on DNA, genes or enzymes.
• Synthesis and Evaluation of Major Non cancer Effects: A synthesis of the all the studies on non cancer effects in the above subchapters to determine the major studies and what effects are seen in these studies.
• Evaluation of Carcinogenicity: An evaluation of all the studies on cancer identified in the above subchapters and a determination of the cancer classification for the chemical (see Appendix 1).
• Susceptible Populations and Life Stages: Determination of what subgroups (such as children or the elderly) may be particularly sensitive to the health effects of the chemical.

Dose-Response Assessment

• Oral RfD: (Choice of study to derive RfD and calculation of value, see Appendix 1)
• Inhalation RfC: (Choice of study to derive RfC and calculation of value, see Appendix 1)
• Uncertainties in the RfD and RfC: Areas of uncertainty in deriving the health values, such as the model used, uncertainty factors, or using animal data to derive a human value.
• Cancer Assessment: (Choice of study to derive cancer values and calculation of values, see Appendix 1).

Major Conclusions in the Characterization of Hazard and Dose-Response

• Human Hazard Potential: On-going studies and suggestions for additional studies.
• Dose Response: A summary of the health values presented in the Dose-Response chapter.

It is evident that hazard identification plays a major role contributing to the slow pace of the assessments. These are lengthy documents that take a long time to prepare. Some assessments, such as on arsenic and formaldehyde (see Appendix 1), have been in preparation for over 20 years, while even the faster documents rarely take less than 5 years to prepare.

Analyze Process to Find Defects

The key defect in this sub process is the length of time it takes to produce these documents. These lengthy documents divert attention away from the objective of IRIS; i.e. to produce health values used by all the offices at EPA and others. Instead, a significant amount of time is spent on issues that are only tangentially, if at all, related to this objective. The following are the steps involved in producing the first draft of the Toxicological Review documents:

• Carry out broad literature search on chemical.
• Examine the titles and abstracts resulting from the literature search to determine how many are actually relevant.
• Of the relevant articles, sort them based on relevance to individual chapters.
• Review each article to determine quality.
• Read the articles and extract the relevant data into a background database and document.
• Synthesize articles into document form.
• Determine relevant studies for health values.
• Derive health values.
• Begin review process.

The scope of these documents was determined by academic scientists and are not focused on the objectives of IRIS; i.e., to derive health values for a chemical. This is because academic scientists spend years studying the intricate details of the workings of chemicals and their worldview is not consistent with the objective of IRIS. To build a better process that leads to greater output, a truncated version of hazard identification should be carried out. This would consist of only identifying those studies that are directly related to deriving the health values for the chemical. There is no need for a background document summarizing all the available information on the chemical – a summary of relevant references is sufficient and would greatly reduce the amount of time needed to carry out this sub process.

Dose-Response Assessment

The dose-response assessment, consisting of the derivation of the health values, is presented separately in the IRIS database and also appears in the Dose-Response chapter of the Toxicological Review document (see above). This section will discuss the actual IRIS health values that are derived and why they are sometimes controversial.

Measure Performance

IRIS values have been criticized as being excessively low, overstating the risks posed by certain chemicals, and not making sense in real world situations.

The following are some examples of these IRIS values:

Formaldehyde

EPA's proposed cancer risk levels for formaldehyde are: 0.8 ppb (1 in 10,000 increased risk); 0.08 ppb (1 in 100,000 increased risk); 0.008 ppb (1 in 1,000,000 increased risk) [13]. These values have been criticized because they are so low that they are less than the levels naturally exhaled in human breath. In fact, in 2018 the American Chemistry Council published a page on its' website with the title, "Our breath causes cancer. Really? Of course not. EPA's revised draft IRIS assessment must be scientifically sound and pass a reality check" [14]. This IRIS value has proven to be so controversial that in 2018, EPA suspended its work on the IRIS Toxicological Review of Formaldehyde [15].

Methanol

EPA's RfD for methanol is 2 mg/kg/day [16]. The average concentration of methanol in: fruit juices ranges from 1-640 mg/L with an average of 140 mg/L; beer ranges from 6-27 mg/L; wine ranges from 96-321 mg/L; distilled spirits ranges from 10-220 mg/L; and fruits is approximately 1000 mg/day [17]. Converting EPA's RfD to a comparable value in mg/L results in a value of 70 mg/L which is less than the average concentration cited above in fruit juices, wine, distilled spirits, and fruits.

Selenium

EPA's RfD for selenium is 0.005 mg/kg/day or 350 µg/day [18]. Selenium is an essential element with a Recommended Daily Allowance (RDA) of 55 µg/day for adult men and 45 µg/day for adult women [19]. The actual estimated dietary selenium intake in the U.S. ranges from 60 to 234 µg/day. The RfD has been criticized because there is no evidence that it is anywhere near the level that could actually cause harm in humans. According to one expert, "For some apparently healthy individuals, however, selenium intake appears to be greater than the RfD, with no adverse signs" [20]. In addition, since selenium is an essential element and is also known to have anti-carcinogenic properties, some scientists believe that cancer rates would decline if the intake of selenium was increased in the general population [21].

The main reason for the low values is the methods EPA uses to calculate them:

- For the RfC and the RfD, EPA divides a concentration level from a human or an animal study by an uncertainty factor ranging from 3 to 1,000. For animal studies, EPA almost always uses an uncertainty factor of 100 or 1,000 which results in a very low level.
- For the cancer risk levels, EPA uses models that extrapolate from the concentration levels in the studies to lower levels that are not part of the study. There are many different models to choose from, and the choice of the model can result in very different results. EPA often uses the "multistage linear" model which is very conservative and results in very low levels.

Analyze Process to Find Defects

The root cause of the defects in this step of the process that there is a disconnect between the process for deriving the health values on IRIS and the way they are actually used in the real world. As noted by EPA, the health values are only intended to provide "an estimate, with uncertainty spanning perhaps an order of magnitude" of the level of the chemical that would not present harm to humans after a lifetime of exposure" [1]. These levels were never intended to be a bright line separating harm vs. safety. EPA believes that "real-world" considerations should be factored in during the last two steps of a full risk assessment (exposure assessment and risk characterization). However, full risk assessments are rarely carried out and often the values presented on IRIS are used as "bright line" values. In summary, practical and real-world situations are not taken into account in the derivation of the values, leading to situations, such as outlined above, where the health values are less than the levels commonly found in food, drinks, or produced in the body.

Review Process

Measure Performance

The current IRIS process calls for the following reviews of the IRIS assessment:

- Intra-EPA review
- Interagency review
- Expert review
- Public review
- Scientific review
- Review of revised document

Analyze Process to Find Defects

This lengthy review process is not necessary and is at the core of what is a broken process. One review should be sufficient to identify issues with the health values.

Congressional Frustration

These and other controversies over the values posted on IRIS have resulted in the U.S. Congress becoming involved in issues about IRIS. In 2017, hearings were held in Congress on IRIS, with a partisan split between Republicans who criticized EPA for not making changes to IRIS as suggested by the NRC in a 2014 report [22] and Democrats who praised EPA for significantly improving

the IRIS program in a short period of time [23].

In 2018, a bill was introduced in Congress – Improving Science in Chemical Assessments Act (H.R. 6468) [24]. This bill calls for:

- Risk assessments to no longer be carried out by the IRIS office and instead to be carried out by individual EPA offices.
- Toxicity values to "include a range of point estimates of risk as well as sources and magnitudes of uncertainty associated with the estimates."
- The establishment of a chemical hazard identification and dose-response steering committee to ensure that there is no duplication of effort between EPA offices or other Federal, State, or international offices in setting toxicity values.

The frustrations with IRIS that led to the introduction of this bill are clearly understandable. But a fundamental defect of this bill is the idea of each individual EPA office using their own data sources to develop health values. This will only lead to more confusion within EPA and frustration by the States, local health departments, and industry. The solution is to develop a process that is both consistent and where outcomes can be tracked. The legislation does propose a dose-response steering committee to avoid duplication of effort. Although a steering committee can avoid some duplication of effort, it will not eliminate the defect of use of differing data sources and procedures that inevitably will happen with individual office fiefdoms. The regrettable reality is that movement at EPA today is often driven by court orders, and these pressures will inevitably lead to individual offices moving forward without waiting for a steering committee to meet and make decisions. In addition, the bill calls for including a range of point estimates of risk and magnitude of uncertainty. Although this sounds reasonable, it will not be useful to the users of IRIS, as presenting a range of values is confusing and does not give them the guidance they seek on environmental chemicals. IRIS already presents the magnitude of uncertainty by presenting confidence levels in the health values (see Appendix 1) and this has not been helpful to IRIS users.

Improve the Process by Addressing the Root Causes You Found

The last step of the Six Sigma Methodology is to improve the entire process by addressing the root causes. The emphasis today in IRIS is on developing "perfect" health values based on an in-depth analysis of all the scientific information available. This needs to be changed: the focus should be on IRIS as a practical database that meets the needs of its users. To achieve this, it needs to greatly increase its output. The focus of IRIS should be on a process that draws upon a diverse group of individuals who actually use the data on IRIS. In order to accomplish this, the sub processes would no longer be conducted by EPA's ORD, but instead would be conducted by a new collaborative initiative overseen and funded by EPA's ORD. A charter would clearly state that the objective of the initiative is to develop health values in a timely fashion focused on IRIS' diverse users while retaining a consistent database. The initiative would consist of scientists both within and outside of EPA. One suggestion for involving scientists outside of EPA would be to involve a private group association, such as the Chemical Industry Institute of Toxicologists (CIIT) . The scientists involved in this initiative would not be expert scientists on individual chemicals but instead would be risk assessment specialists, i.e. scientists who are experienced in evaluating data and developing risk values on a broad variety of chemicals. Expert scientists are not trained to do risk assessment, instead they often deal with multi-year projects on their very focused areas of expertise, and they will not be effective at reaching the goal of developing health values in a timely fashion.

Summary of New Process

In summary, the new IRIS process would consist of:

Identify Chemicals

An IRIS Advisory Group would be set up consisting of actual users of IRIS, such as individuals from States across the country and local health departments, industry representatives, and other Federal Agencies. A Federal Register would also go out asking for nominations of chemicals by the public. The IRIS Advisory Group would meet approximately twice a year to develop a list of priority chemicals for IRIS assessments based on their experience and the nominations from the public.

A Collaborative IRIS Initiative

would be set up consisting of scientific working groups consisting of scientists both within and outside of EPA with a wide range of backgrounds, but all with experience in risk assessment. The purpose of having scientists with differing backgrounds is that this will enhance differing points of view being set forth and dealt with at the beginning of the process, instead of at the end of the process which results in delays.

Hazard Identification

A team of approximately 6 scientists would be responsible for identifying relevant studies. Hazard identification would consist of only identifying those studies that are directly related to deriving the health values for the chemical. There would not be Toxicological Review Documents or lengthy summaries of studies, instead a table would be prepared consisting of the basic information about each study considered to be the critical study for deriving the health values.

Dose-Response Assessment

The team would be responsible for deriving a health value for a chemical within approximately 180 days. Since the team members are from a diverse set of backgrounds, different points of view would be brought up and negotiated from the beginning of the process, instead of waiting until after the values are finalized. In addition, a reality check would be done on each of the health values to ensure that the values work in real-world situations. These values should be analyzed considering the fact that full risk assessments are rarely carried out and these are the values that States and others will be using in the real world. If consensus

on one value is not possible, the team could develop more than one health value and all of these values would be posted on IRIS and reviewed.

Review Process

The initial health value would be posted on IRIS for 45 days. Two scientists from within the IRIS initiative would be responsible for reviewing the value and submitting comments. In addition, IRIS would seek public comments on the value during the same 45 days. The initial team of 6 scientists would review the comments and make changes to the health value as needed, within 45 days.

Post on IRIS

The revised health value would be posted on IRIS.

This new process would collapse the current multi-year IRIS assessment project into a target of 6-9 months' time.

See Figure 5 for a summary of the suggested new IRIS process.

See Appendix 1 for an example of an IRIS posting using the new process.

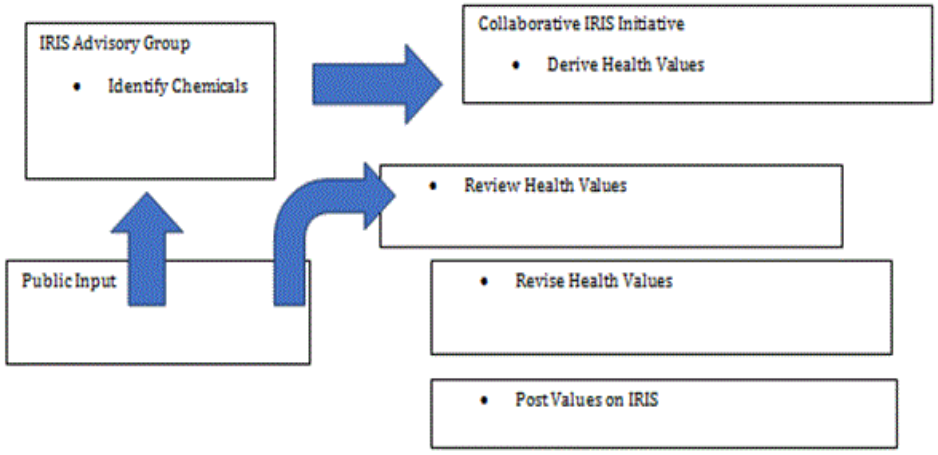

Figure 5: Suggested new IRIS process

Conclusions

If EPA is to remain a central hub of data, science, and guidance, in a society that is becoming more environmentally conscious, then radical reform that focuses on getting users timely, understandable, and useful consistent data is essential. The current IRIS process has important chemicals like formaldehyde and arsenic taking 30 years and counting, which on its face is a failure and has led to EPA no longer being seen as the leadership hub for environmental information. Lost in the failure is the fact that the initial intent of IRIS, which was to achieve a single consistent database, is a goal worth retaining. The purpose of this article was to present a significantly different process and focus for IRIS while retaining the concept of a single database. If EPA is to reassume a leadership role in environmental guidance and standard setting, it must adopt a process worthy of the 21st century which is transparent and far more collaborative, with a focus on speed and on the end user. The Six Sigma Framework was used as a tool to return IRIS to its effective historical origins based on removing defects and focusing on speed of results to the end user. It is our hope that this article will open up a constructive dialogue that will result in States and localities getting more information in a timelier manner.

Abbreviations

BMC: Benchmark concentration
BMD: Benchmark dose
CAAC: Chemical Assessment Advisory Committee
CIIT: Chemical Industry Institute of Toxicologists
EPA: Environmental Protection Agency
EPCRA: Emergency Planning and Community Right to Know Act
GAO: Government Accountability Office
GD: Gestation Day
IRIS: Integrated Risk Information System
IUR: Inhalation Unit Risk
LOAEL: Lowest-Observed-Adverse-Effect Level
NOAEL: No-Observed-Adverse-Effect Level
NRC: National Research Council
NTP: National Toxicology Program
OMB: Office of Management and Budget
ORD: Office of Research and Development
OSF: Oral Slope Factor
RfC: Reference Concentration
RfD: Reference Dose
SAB: Science Advisory Board
TSCA: Toxic Substances Control Act

APPENDIX 1 – ADDITIONAL DETAILS ON IRIS ASSESSMENTS

FURTHER DETAILS ON HEALTH VALUES

Hazard Identification

Hazard identification consists of review of the literature (consisting primarily of human studies, i.e., epidemiology and

animal studies) to determine the health effects from exposure to the chemical. The health effects are divided into two types: non cancer and cancer effects. The major non cancer effects studied are on the brain (neurological), kidney (renal), liver (hepatic), stomach (gastrointestinal), and reproductive systems. Cancer effects consist of any types of tumors that result from exposure to the chemical.

Dose-Response Assessment

Dose-response assessment consists of selecting the studies that will be the basis for the health values and deriving the health values for the chemical. In IRIS, the dose-response assessment is termed the "Chemical Assessment Summary" and is divided into two sections: non cancer assessment and cancer assessment [1].'

Non cancer Assessment section

This section contains two health values, one for exposure to the chemical through inhalation (breathing it in air) and another for exposure to the chemical through oral exposure (ingesting it in drinking water). These values are calculated to be very conservative; i.e. to be protective of all individuals, including "sensitive subpopulations" including young children, the elderly, and persons with preexisting health conditions [1].

Health Value for Inhalation Exposure Reference Concentration (RfC)

The EPA definition is, "An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observedadverse-effect level (LOAEL), or benchmark concentration (BMC),with uncertainty factors generally applied to reflect limitations ofthe data used" [1]. In plain English, the RfC is an estimate of the level of a chemical, if breathed in air over a lifetime (estimated at 70 years) that would not result in adverse health effects.

Study selection

The RfC is based on the identification of a "critical" study in humans (epidemiology) or laboratory animals. This study is selected using the hazard identification step of the risk assessment process to identify all the relevant non cancer inhalation studies. These studies are reviewed and a study is selected as the "critical study" based on the following criteria:

• Species studied - Epidemiology studies are preferred; animal studies (usually in rats or mice) are used if epidemiology studies are not available.
• Length of study – Since the RfC is intended to be protective over a lifetime of exposure, longer studies are considered more appropriate then shorter studies. For epidemiology studies, multi-year studies are considered better than studies less than 1 year in length; for animal studies, 2-year studies are considered optimal, although shorter length studies are used if longer term studies are not available.
• Dose levels – Studies in which defined levels of the chemical are studied, at multiple doses, are preferred over studies with undefined dose levels or only one dose.
• Effects studied – The effects being investigated in the study need to be relevant to human exposure. For example, some effects on the rat kidney have been shown not to be relevant to humans.
After the critical study is selected, the highest concentration in the study where adverse effects were not observed (NOAEL), the lowest concentration at which adverse health effects were observed (LOAEL), or modeling all the concentration levels to determine a benchmark concentration (BMC) is carried out. An uncertainty factor ranging from 3 to 1,000 is the applied to the NOAEL, LOAEL, or BMC. This uncertainty factor is applied to address the uncertainties surrounding the concentration level (NOAEL, LOAEL, or BMC) selected from the critical study to be protective for the general human population. Therefore, a smaller uncertainty factor (3-10) is usually applied to epidemiology studies while a larger uncertainty factor (100-1,000) is usually applied to animal studies. In addition, the length of the study is also a factor in determining the uncertainty factor; smaller uncertainty factors are applied to longer studies and larger uncertainty factors applied to shorter studies.

Example: RfC for Acetaldehyde

Two studies in rats who breathed air containing acetaldehyde at various concentrations for 4 weeks showed no adverse effects on the respiratory system at 8.7 mg/m^3. The value is rounded to 9 mg/m^3 and is divided by an uncertainty factor of 1,000: 9 $mg/m^3/1000$ = 0.009 mg/m^3 (the RfC for acetaldehyde) [25].

Health Value for Oral Exposure Reference Dose (RfD)

The EPA definition is, "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose (BMD), with uncertainty factors generally applied to reflect limitations of the data used" [1]. The plain English explanation of the RfD is the same as the RfC (see above), except that it is the level of a chemical ingested in water over a lifetime that would not result in adverse health effects. The criteria for study selection are the same as discussed above for the RfC.

Example: RfD for Acetone: A study in rats that ingested water containing acetone at various concentrations for 13 weeks showed no effects on the kidney at 900 mg/kg/day. The value is divided by an uncertainty factor of 1,000: 900 mg/kg/day/1,000 = 0.9 mg/kg/day (the RfD for acetone) [26].

The non-cancer assessment section in IRIS also contains a

summary of the studies that were used as the basis for the RfC or RfD; a discussion of how the values were derived, including the calculations; a discussion of how the uncertainty factor was selected; and confidence levels in the RfC or RfD – each value is ranked as either low, medium, or high in three areas: the study used as the basis for the value, the overall database for the chemical, and the overall RfC or RfD.

Most chemicals do NOT have both an RfC and RfD; the determination as to which to calculate is based on the available data and which is the most important exposure route. For example, a chemical such as acetaldehyde (see RfC discussion above) that easily volatilizes in air and is not commonly found in water has an RfC and not an RfD. Alternatively, acetone (see RfD discussion above), a chemical that is more commonly found in water and does not easily volatilize in air has an RfD and not an RfC.

Cancer Assessment section

The cancer assessment section contains cancer descriptors (weight-of-evidence assessment of the likelihood that the chemical will cause cancer) and a summary of the studies used to assess the weight of evidence that were identified in the hazard identification step of the process [1].

Cancer Descriptors

- Cancer Descriptors characterize the chemical as:
    - Carcinogenic to humans
    - Likely to be carcinogenic to humans
    - Suggestive evidence of carcinogenic potential
    - Inadequate information to assess carcinogenic potential
    - Not likely to be carcinogenic to humans

If the chemical is considered "carcinogenic to humans" "or likely to be carcinogenic to humans", the cancer assessment section may contain one or two subsections: "Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure" and/or "Quantitative Estimate of Carcinogenic Risk from Oral Exposure." These sections contain health values that are estimates of the increased risk of developing cancer from exposure to the chemical by inhalation exposure (breathing air containing the chemical) or oral exposure (ingesting water containing the chemical). These health values are only derived if there are sufficient data available that is suitable to be modelled [1].

Quantitative Estimate of Cancer Risk from Inhalation Exposure

- **Inhalation unit risk (IUR)**

The EPA definition is "An estimate of the increased cancer risk from inhalation exposure to a concentration of 1 $\mu g/m^3$ for a lifetime. The IUR can be multiplied by an estimate of lifetime exposure (in $\mu g/m^3$) to estimate the lifetime cancer risk" [1]. The plain English explanation of the IUR is that it presents an estimate of the increase in cancer in the human population after inhaling air containing the chemical at a specified level over a lifetime (estimated at 70 years).

- **Air concentrations at specified risk levels**

The IUR is then converted to air concentrations that show an increase in cancer risk of one additional cancer per 10,000 persons, one additional cancer per 100,000 persons, and one additional cancer per 1,000,000 persons.

These air concentrations are significant because they are often used in the last step (risk characterization) of the risk assessment to decide what level of the chemical is considered "acceptable". Generally, EPA considers concentration of a chemical associated with the risks cited above of one additional cancer per 10,000, 100,000, or 1,000,000 persons to be "unacceptable" for regulation-setting purposes, while concentrations of a chemical associated with lesser risk are generally considered "acceptable".

Example

Benzene - Many epidemiology studies have shown an increase in cancer in workers exposed to benzene in the air. One of these studies is selected to represent the best available data. A model is used to extrapolate from the concentrations of benzene to which the workers were exposed and the resulting cancer in the workers to lower concentration levels of benzene that may be present in the environment. This model estimates how many extra cases of cancer would occur if persons in the general population inhaled air containing benzene at a very low level ($1 \mu g/m^3$) over their lifetime. For benzene, the IUR ranges from 2.2×10^{-6} to 7.8×10^{-6}. The air concentrations at specified risk levels are: 13.0 to 45.0 $\mu g/m^3$ (1 in 10,000 increased risk); 1.3 to 4.5 $\mu g/m^3$ (1 in 100,000 increased risk); 0.13 to 0.45 $\mu g/m^3$ (1 in 1,000,000 increased risk) [27].

Quantitative Estimate of Cancer Risk from Oral Exposure

- **Oral slope factor (OSF)**

The EPA definition is: "An estimate of the increased cancer risk from oral exposure to a dose of 1 mg/kg-day for a lifetime. The OSF can be multiplied by an estimate of lifetime exposure (in mg/kg-day) to estimate the lifetime cancer risk" [1]. The plain English explanation of the OSF is that it presents an estimate of the increase in cancer in the human population after ingesting water containing the chemical at a specified level over a lifetime (estimated at 70 years).

- **Water concentrations at specified risk levels**

The OSF is then converted to water concentrations that show an increase in cancer risk of one additional cancer per 10,000 persons, one additional cancer per 100,000 persons, and one additional cancer per 1,000,000 people.

Example

Benzene - The OSF for benzene was calculated based on the same study and model used to calculate the IUR for benzene (see discussion above). The IUR is converted to an OSF by multiplying

the IUR by conversion factors . For benzene, the OSF ranges from 1.54 x 10^{-5} to 5.45 x 10^{-5} per µg/kg/day. The drinking water concentrations at specified risk levels are: 1000 to 10,000 µg/L (1 in 10,000 increased risk); 10 to 100 µg/L (1 in 100,000 increased risk); 1 to 10 µg/L (1 in 1,000,000 increased risk) [27]. These risk levels are used in the same manner as the air concentrations at specified risk levels (see discussion above). Both the air and water specified risk levels are calculated using mathematical models that take the results from epidemiology studies or cancer bioassays (animal studies lasting 2 years in length) and model the results to estimate the level of risk in the human population. The selection of the study to model and which model to use (there are a large number of scientifically valid models that have been developed) can result in results that vary widely. There is rarely scientific consensus on these issues.

Similar to the non cancer assessment, most chemicals do not have both an IUR and OSF; they are calculated based on the available data and the importance of the exposure route. The example above for benzene demonstrates a chemical that has both an IUR and OSF. This is because there is a great deal of data showing the relationship between benzene and leukemia.

Both non cancer and cancer sections

If a chemical has both non cancer values and cancer values available on IRIS, EPA will usually use the cancer value in the last two steps (exposure assessment and risk characterization) of the risk assessment, since cancer is considered the more sensitive endpoint. A Toxicological Review document is also available on IRIS for all chemicals assessed after 1996 (see Table 1). This document is "intended to provide scientific support and rationale for the hazard and dose-response assessment provided in IRIS pertaining to chronic exposure to the chemical" [1].

EXAMPLES OF CHEMICALS ON IRIS

Arsenic

Arsenic is an example of a chemical that EPA has been working on for over 30 years and has been under revision on IRIS for more than 20 years.

1988: EPA reassesses the cancer data associated with the ingestion of inorganic arsenic.

1991: EPA derives the RfD for arsenic.

1995: EPA derives the cancer risk estimates for arsenic.

2005: EPA prepares draft "Toxicological Review of Inorganic Arsenic in Support of Summary Information on IRIS".

2007: Science Advisory Board (SAB) Arsenic Review Panel reviews 2005 draft Toxicological Review of Arsenic.

2010: EPA prepares revised draft "Toxicological Review of Inorganic Arsenic in Support of Summary Information on IRIS" in response to the SAB comments from 2007 and submits it for another review by the SAB Arsenic Review Panel. EPA announces it in the Federal Register with a 60-day public comment period.

2011: Congress mandates that the National Research Council (NRC) conduct an independent peer review of the arsenic assessment before EPA finalizes the assessment.

2013: The NRC holds a public workshop on critical scientific issues on arsenic and prepares a report calling for the EPA to use systematic review and mode-of-action data to support its toxicologic assessment.

2014: EPA releases the draft literature searches and preliminary evidence tables that it plans to use in development of the draft IRIS assessment for arsenic.

2018: The NAS holds a workshop to discuss strategies and tools used by IRIS for conducting systematic reviews of mechanistic data in IRIS assessments (although this workshop is not specifically on arsenic, it discusses some of the issues raised by the NRC in 2013).

2019: The NAS holds a workshop on the Systematic Review Protocol for the IRIS assessment on arsenic.

Formaldehyde

Formaldehyde is an example of a chemical that EPA has been working on for 30 years. EPA has currently suspended work on the IRIS Toxicological Review of Formaldehyde.

1989: EPA derives the cancer risk estimates on IRIS.

1990: EPA derives the RfD on IRIS.

2003: EPA prepares "IRIS Toxicological Review and Risk Characterization of Formaldehyde/Vinyl Acetate/Acetaldehyde: Based on Mode of Action".

2010: EPA prepares external review draft "IRIS Toxicological Review of Formaldehyde (Inhalation)".

2011: The NRC reviews the external review draft "IRIS Toxicological Review of Formaldehyde (Inhalation)". The NRC notes some recurring methodological problems in the assessment and concludes that the assessment was not prepared in a consistent fashion and does not contain sufficient documentation on methods used to identify and evaluate studies in the risk assessment.

2014: EPA holds public workshop – "State-of-the-Science Workshop to Discuss Issues Relevant for Assessing the Health Hazards of Formaldehyde Inhalation".

2018: EPA suspends the IRIS Toxicological Review of Formaldehyde.

EXAMPLE IRIS POSTING USING NEW PROCESS

The following is an example of an IRIS assessment under the new process based on the current IRIS Assessment for Acrylic Acid and the EPA Provisional Peer-Reviewed Toxicity Values for Acrylic Acid [28, 29].

Studies Considered for RfC				
Reference	Species/Study Type	Length of study	Exposure Concentrations	Effect/concentration level
Miller et al. 1981	F344 rat/subchronic	13 weeks	0, 5, 25, 75 ppm	Degeneration of the nasal epithelium/75 ppm
Miller et al. 1981	B6C3F1 mouse/subchronic	13 weeks	0, 5, 25, 75 ppm	Decreased body weight, degeneration of the nasal epithelium/5 ppm
Klimisch and Hellwig, 1991	SD rat/developmental	Gestation Days (GD) 6-15	0, 39.4, 114.0, 356.2 ppm	No effects were observed on fetal development
Saillenfait et al., 1999	SD rat/developmental	GD 6-20	0, 50, 100, 200, 300 ppm	Decreased fetal body weight/300 ppm
Neeper-Bradley et al., 1997	New Zealand rabbit/ developmental	GD 6-18	0, 25, 75, 225 ppm	No effects were observed on fetal development

Study selected as basis of RfC = Miller et al. 1981 (mouse) because it was the longest study available that used multiple doses and examined a number of endpoints.

RfC Calculations = 5 ppm (LOAEL) x 72.06 (molecular weight)/24.12 = 14.94 mg/m^3

LOAEL adjusted because study was 6 hours/day, 5 days/week = 14.94 mg/m^3 x 6 hours/24 hours x 5 days/7 days = 2.67 mg/m^3

LOAEL calculated for a gas/respiratory effect in the extra thoracic region = 0.33 mg/m^3

RfC = 0.33 mg/m^3 / 300 (Uncertainty Factor) = 0.001 mg/m^3

Basis for Uncertainty Factor =

- 10-fold to protect sensitive human subpopulations
- 3-fold for extrapolation from subchronic to chronic duration
- 10-fold for interspecies extrapolation and use of a LOAEL

Studies Considered for RfD				
Reference	Species/Study Type	Length of study	Exposure Doses/Route	Effect/Dose level
DePass et al., 1983	F344 rat/subchronic	90 days	0, 83, 250, 750 mg/kg-day/ drinking water	Reduced body weight gain/250 mg/kg-day
Hellwig et al., 1993	Wistar rat/subchronic	90 days	0, 150, 375 mg/kg-day/ gavage	Death/375 mg/kg-day (15/20 rats)
Hellwig et al, 1993	Wistar rat/chronic	26-28 months	0, 8, 28, 78 mg/kg-day/ drinking water	No effects were observed
Hellwig et al., 1997	Wistar rat/developmental	70-98 days premating, mating, gestation, lactation	0, 53, 240, 460 mg/kg-day/ drinking water	Reduced pup weight/240 mg/kg-day
DePass et al., 1983	F344 rat/developmental	13 weeks premating, mating, gestation, lactation	0, 83, 250, 750 mg/kg-day/ drinking water	Reduced pup weight/750 mg/kg-day
McCarthy et al., 1992	CD-1 mouse/Dominant lethal assay	5 daily doses	0, 16, 54, 162 mg/kg-day/ gavage	No effects were observed

Study selected as basis of RfD = Hellwig et al. 1997 because it was a two-generation developmental study with multiple doses that examined a number of endpoints.

RfD Calculations = 53 mg/kg-day (NOAEL) / 100 (Uncertainty Factor) = 0.5 mg/kg-day

Basis for Uncertainty Factor =

- 10-fold to protect sensitive human subpopulations
- 10-fold for interspecies extrapolation and use of a LOAEL

Cancer Assessment

The Only cancer study available is Hellwig et al., 1993 where no tumors were observed in rats after chronic exposure to acrylic acid in drinking water. However, since this is only one study and the maximum tolerated dose may not have been reached, acrylic acid is classified as: Inadequate information to assess the carcinogenic potential

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