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Prioritizing Pathogens for Potential Future Regulation in Drinking Water

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A method alternative to the EPA's determination of microorganisms of regulatory concern for drinking water quality is proposed.

SHUTTERSTOCK

Drinking water in the U.S. is among the safest in the world but outbreaks of disease linked to drinking water still occur. For example, from 1991 to 2002 there were 183 reported waterborne disease outbreaks caused by chemical contaminants (16%), viruses (8%), bacteria (17%), protozoa (21%), and unidentified agents of acute gastrointestinal illness (38%) (*1*). The majority of these outbreaks were linked to groundwater (76%) with surface water accounting for 18%. Water in these outbreaks was provided by community systems (36%), noncommunity systems (39%), and individual wells (25%), and outbreaks were associated with untreated groundwater (32%), treatment failures or deficiencies (32%), and problems in the distribution system (23%). It has been estimated that annually in the U.S., up to 19.5 million cases of all types of illnesses may be associated with contaminated drinking water (*1*), 4.3−11 million cases of which are acute gastrointestinal illness (*2*). Consequently, water suppliers and regulators expend considerable effort and resources to ensure the safety of and improve the quality of drinking water through enhanced treatment strategies and technologies, and stricter regulations.

The Contaminant Candidate List. Under the Safe Drinking Water Act Amendments of 1996 the U.S. Environmental Protection Agency (EPA) must develop and publish a contaminant candidate list (CCL) identifying contaminants (and groups of related contaminants) that are currently unregulated in drinking water and that may pose risks to public health. The amendments specifically require EPA to consider the following criteria to determine whether a contaminant may require listing on the CCL: (1) the contaminant may have an adverse effect on the health of persons; (2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and (3) in the sole judgment of the EPA Administrator, regulation of such a contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems. The CCL is not a regulation itself. Rather, it is a determinative process; EPA must decide whether or not to regulate at least five CCL contaminants with a National Primary Drinking Water Regulation. The 1996 Safe Drinking Water Act amendments require that the CCL is reviewed and revised every 5 years. The first CCL (CCL1) was published in March 1998 (*3*), CCL2 was published in February 2005 (*4*), and the draft CCL3 was published for public comment in the Federal Register on February 21, 2008 (*5*). Table 1 lists all microbial contaminants included on the previous two CCLs, the current draft CCL3, and those selected by an alternative approach, which is described in this paper.

It is noteworthy that all of the required regulatory determinations to date have been decisions to not regulate CCL contaminants, including the microbe *Acanthamoeba* from CCL1 (*6*) and 11 contaminants from CCL2 (*7*). The recurring determination that none of the CCL pathogens listed during the last 11 years should be regulated, or lack sufficient information to make a regulatory determination, raises questions regarding the effectiveness of the CCL process

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TABLE 1. Microbes on the Contaminant Candidate List[a]

EPA CCL1, 1998	EPA CCL2, 2005	EPA Draft CCL3, 2008	Alternate microbial CCL3 (this paper)
Acanthamoeba			
Adenoviruses	Adenoviruses		
Aeromonas hydrophila	*Aeromonas hydrophila*		
Caliciviruses	Caliciviruses	Caliciviruses	Caliciviruses (Norovirus)
		Campylobacter jejuni	*Campylobacter*-like organisms[b]
Coxsackieviruses	Coxsackieviruses		
Cyanobacteria (blue-green algae), other freshwater algae, and their toxins[c]	Cyanobacteria (blue-green algae), other freshwater algae, and their toxins[c]		
		Entamoeba histolytica	
Echoviruses	Echoviruses		
			Enteroviruses (includes coxsackieviruses and echoviruses)
		Escherichia coli O157	Toxigenic *Escherichia coli*[d]
Helicobacter pylori	*Helicobacter pylori*	*Helicobacter pylori*	
		Hepatitis A virus	Hepatitis A virus
		Legionella pneumophila	*Legionella pneumophila*
Microsporidia	Microsporidia		
Mycobacterium avium	*Mycobacterium avium*		*Mycobacterium avium*
		Naegleria fowleri	
			Rotavirus
		Salmonella enterica	*Salmonella enterica*[e]
		Shigella sonnei	*Shigella* spp.[e,f]
		Vibrio cholerae	*Vibrio cholerae*[e]

[a] See the Supporting Information for a brief description of all PCCL pathogens. [b] The microbial workgroup expanded *Campylobacter jejuni* to include *Campylobacter*-like organisms such as *Arcobacter*, which was not distinguished from *Campylobacter* until recently (*23*), but was evaluated separately by EPA on the PCCL (*5, 15*). [c] Moved to the chemical list of contaminants for the draft CCL3. [d] The microbial workgroup expanded their evaluation of *Escherichia coli* beyond O157 and included other waterborne, toxigenic *E. coli* of public health significance (*24*). [e] Removed following postscoring evaluation. [f] The workgroup expanded their evaluation of *Shigella sonnei* to *Shigella* spp.

in identifying and listing microbial contaminants for potential regulation in drinking water and the role of the CCL in EPA's overall drinking water program.

Following publication of the first CCL, EPA sought advice from the National Research Council (NRC) on how to improve the CCL process for the development of future lists. The resultant Committee on Drinking Water Contaminants recommended a broad, transparent, and reproducible process beginning with the identification of the "universe" of potential drinking water contaminants that could subsequently be assessed and culled to a preliminary CCL (PCCL), which would be further characterized to identify a future CCL (*8*). In 2002, EPA tasked the National Drinking Water Advisory Council (NDWAC) with assessing the feasibility of implementing the NRC's recommendations. The NDWAC subsequently supported the NRC approach and recommended several overarching principles that EPA should use to develop future CCLs, such as the need to integrate expert judgment throughout the CCL process (*9*).

In accordance with the NRC and NDWAC recommendations, the EPA identified the microbial universe for CCL3 by combining a list of 1415 human pathogens (bacteria, viruses, protozoa, helminths, and fungi) compiled by Taylor et al. (*10*) with 6 additional fungi and reovirus that had been identified in a literature review. In response to EPA's request for nominations (*11*), additional microorganisms were added (e.g., *Methylobacterium* spp., Mimivirus) bringing the microbial universe to 1425 microorganisms (*12*). A series of 12 screening criteria was then used to exclude pathogens with biological properties that are incompatible with water transmission by ingestion, inhalation, or dermal contact, and those pathogens that are typically transmitted by sources other than drinking water (e.g., pathogens transmitted solely by respiratory secretions). This screening process resulted in the exclusion of 97.8% of the microbial universe and the remaining 29 pathogens were moved to the PCCL (*13*).

The EPA devised a scoring system based on waterborne disease outbreaks, occurrence of the pathogen in water, and adverse health effects to score and rank the PCCL microbes. The higher of the outbreak or occurrence scores was added to the health effects score to produce a composite pathogen score. A series of expert workshops were convened by the EPA to review, discuss, and comment on the microorganisms considered and selected for the draft CCL3 and to help score the attributes of outbreaks, occurrence, and health effects for each PCCL microbe (*14*). Based on a "natural" but arbitrary break-point in the overall ranked scores, the 11 top-ranked pathogens were moved onto the draft CCL3 (Table 1). However, it is not clear whether any experts were consulted to provide a subsequent evaluation of the scored PCCL pathogens to confirm the appropriateness of the scoring, and whether the inclusion of a pathogen on the CCL3 would constitute a meaningful opportunity for health risk reduction. A description of the EPA approach to evaluate PCCL microorganisms for inclusion or exclusion from the draft CCL3 can be found in the Federal Register notice (*5*) and in *Contaminant Candidate List 3 Microbes: PCCL to CCL Process* (*15*). Additional technical support documents for the draft CCL3 (and CCL1 and CCL2) are likewise available (*16*).

An Alternative Approach for Developing the CCL. In early 2008, the American Water Works Association (AWWA) convened an independent group of five microbiologists (hereafter referred to as the microbial workgroup; see also Acknowledgments) to develop a response to EPA's request for comments on the draft CCL3 and assess whether alternative approaches should be considered for developing an efficient and transparent process for evaluating and selecting preliminary CCL microbial contaminants to be included on the CCL (Note: we will not refer to this [the microbial workgroup] preliminary CCL as "PCCL" as we discuss a methodological approach as opposed to the official EPA PCCL referenced above.) The background and experience

TABLE 2. Scoring PCCL Pathogens Using the Alternative Approach

PCCL pathogen	outbreak score	occurrence score	health effects score	total
***Escherichia coli* O157**[a]	5	5	4.5	14.5
Legionella pneumophila[a]	5	5	4	14
Shigella spp.	5	5	4	14
Salmonella enterica	5	5	3.5	13.5
***Campylobacter*-like organisms**[a]	5	5	3.5	13.5
Human caliciviruses (Norovirus)[a]	5	3	3.5	11.5
Mycobacterium avium[a]	1	5	3	9
Hepatitis A virus[a]	4	2	2.5	8.5
Rotavirus[a]	3	3	2.5	8.5
Vibrio cholerae	0	3	5	8
Enteroviruses[a]	0	5	2.5	7.5
Naegleria fowleri	1	1	5	7
Yersinia enterocolitica	2	3	2	7
Fusarium solani	0	5	1.5	6.5
Helicobacter pylori	0	3	3.5	6.5
Aeromonas hydrophila	0	5	1.5	6.5
Adenoviruses	0	3	2.5	5.5
Toxoplasma gondii	1	1	3	5
Entamoeba histolytica	1	0	3	4
Cyclospora cayetanensis	0	0	3	3
Hepatitis E virus	0	0	3	3
Plesiomonas shigelloides	0	0	2	2

[a] Should be included on the alternate microbial CCL3 in accordance with the alternative approach and following a postscoring evaluation by the microbial workgroup.

of the workgroup members included public health, environmental microbiology, water quality, and clinical microbiology. An alternative decision tree approach was developed that explicitly, consistently, and transparently uses pertinent published data in conjunction with expert judgment to identify those pathogens whose potential regulation are likely to lead to improvements in public health. This alternative approach uses the best available data to build upon a previously published conceptualized approach by AWWA for constructing the CCL (*17*) and is in accord with the language of the Safe Drinking Water Act Amendments of 1996 as supported by the NRC and NDWAC.

The microbial workgroup presumed that the EPA's universe of 1425 potential microbial contaminants and the process used to screen the universe down to the 29 microbes on the preliminary CCL were both reasonable. Therefore, the workgroup started the attribute scoring process with a subset of the 22 highest ranked preliminary CCL microbes. The remaining seven pathogens were not individually evaluated due to their low scores, or because they were grouped with similar preliminary CCL microorganisms that were ranked; these microbes were *Arcobacter*, *Aspergillus fumigatus*, Astroviruses, *Blastocystis hominis*, *Exophiala jeanselmei*, *Isospora belli*, and microsporidia (*Encephalitozoon* spp. and *Enterocytozoon* spp.).

As for the EPA approach, the alternative approach described in this paper used waterborne disease outbreak data, occurrence information, and health effects to score and rank preliminary CCL pathogens, albeit with key differences and results that are summarized in the following sections. Additional details of the development, application, and results of the scoring methodology for the alternative approach compared to the EPA approach are provided in the Supporting Information (SI) for this paper.

Scoring Waterborne Disease Outbreaks. Waterborne disease outbreak scores (0−5) were determined using a decision tree approach (Figure S1) considering only water intended for use as drinking water or serving as a drinking water source. The questions were designed to most accurately categorize the information available on U.S. (and in some cases U.S. territories) outbreaks for each preliminary CCL microbe evaluated. In scoring waterborne disease outbreaks, the alternative approach used outbreak descriptions published in the U.S. Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report or in peer-reviewed literature. Outbreaks in water used exclusively for recreational purposes (e.g., swimming pools and spas) were excluded.

Scoring Microbial Occurrence. Occurrence scoring (0−5; Figure S2) used peer-reviewed data documenting pathogen occurrence in U.S. waters used for or intended for human consumption. The alternative approach further differentiates occurrence in treated drinking water from occurrence in untreated drinking water taking into account that many pathogenic microorganisms listed on the preliminary CCL (e.g., *Vibrio cholerae*) are known to be easily controlled with routine chlorine disinfection, which is the predominant and widespread operational practice throughout the U.S. Although a large portion of the U.S. population is served by inadequately disinfected—or nondisinfected—groundwater, the recently promulgated EPA Ground Water Rule (*18*) is intended to reduce the risk of illness due to microbial contamination of public groundwater systems.

Scoring Health Effects. Health effects were scored on a scale of 1−5 (Figure S3) and in consultation with a practicing clinical microbiologist. For each microorganism, the most common health outcome for the general population and nonseverely immuno-compromised sensitive subpopulations (e.g., children, pregnant women, elderly individuals) was determined. A single health effects score was developed for the microbe under evaluation. If death was the most common health outcome (e.g., *Naegleria fowleri*) the health effect score was 5. If death was not the most common health outcome, the microbial workgroup subsequently scored five subcriteria (require medical attention to recover, severity, infectious dose, secondary spread, sequellae) to obtain a consensus-based overall health effects score.

Score Summary

The scores from the outbreak, occurrence, and health effects decision trees were added to obtain the overall score and the preliminary CCL microorganisms were ranked from highest to lowest scores, with a maximum possible score of 15. The alternative approach included both outbreak and occurrence

TABLE 3. Key Differences between the Alternative and EPA Approaches[a]

component	issues	alternative approach	EPA approach
waterborne disease outbreaks (WBDOs)	outbreak documentation	U.S. Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR); peer-reviewed publications	CDC MMWR; peer-reviewed publications; conference proceedings, CDC web pages
	definition of WBDO/ magnitude	uses CDC's MMWR WBDO definition (2 or more cases constitutes an outbreak) but score adjusted by number of cases	uses CDC's MMWR WBDO definition but scores not adjusted for number of cases
	location	developed nations using conventional water treatment	developed nations, U.S. territories, undeveloped nations[a]
	time line	none before 1974 (SDWA enactment); advocates 1980 as cutoff	1973 or 1974, beginning with CDC MMWR reports
	frequency	adjusted scores based on <5 or ≥5 outbreaks	pathogens causing ≥2 outbreaks receive higher scores
	water sources	drinking water and drinking water sources	drinking water and drinking water sources; recreational waters including swimming pools and hot tubs
	evidence	pathogen detection by culture; molecular methods; or serological data linked to supporting water quality data	pathogen detection by culture; molecular methods; serological data without supporting water quality data
occurrence	occurrence documentation	CDC MMWRs; peer-reviewed journals	CDC MMWR; peer-reviewed journals; conference proceedings; CDC web pages
	location	developed nations using conventional water treatment	developed nations; U.S. territories; undeveloped nations[b]
	water sources	only considered water used as or for drinking water; finished drinking water occurrence scored higher than occurrence in source water	drinking water and drinking water sources; recreational waters including swimming pools and hot tubs
	detection methods	considered molecular detection and direct culture, however molecular methods were given lower scores than direct culture	equal value for scoring molecular- and culture-based detection
	frequency of detection	higher scores assigned to pathogens that were detected multiple times by independent laboratories	equal scores assigned to single or multiple detection events
health effects	sensitive subpopulation scoring	single health effect score for general and (nonsevere) sensitive subpopulations	scores nonsevere sensitive populations separate from the general population and averages to develop a single normalized score
	background of health effects experts	scored in consult with clinical microbiologist	unknown
scoring	WBDO and occurrence scores	included both WBDO and occurrence scores	included only the higher of the WBDO and occurrence scores
expert review	postscoring evaluation	all scored PCCL microbes evaluated independently by all 5 microbial workgroup members and voted to include or not include (by simple majority) on the alternate microbial CCL3	unknown
	treatability	considered sensitivity of pathogens to conventional treatment	did not consider sensitivity of pathogens to conventional treatment

[a] See the Supporting Information for further information. [b] The EPA approach assigned a higher score to WBDOs occurring in the U.S. or developed nations.

scores (not just the higher of the two scores as is in the EPA approach), provided that the outbreak report was distinct from the occurrence report. Although they are related, they are not synonymous and do not provide the same information—waterborne disease outbreaks are directly related to public health concerns while occurrence data provide an

indication of the presence of the microorganism in water and therefore the *potential* of the microorganism to cause future waterborne disease. Single reports were not used to score both outbreak and occurrence so these parameters were not "double-counted". It is important to score outbreak and occurrence separately given that these pieces of information are likely to be underestimated for a variety of reasons: many outbreaks are either not reported or the causative agent is never identified (*19*); occurrence data may be severely underestimated due to the lack of reliable and sensitive detection methods for many preliminary CCL pathogens.

Selecting a numerical threshold or break-point score above which a preliminary CCL microorganism is included on the CCL is inherently an arbitrary process, but including too many microorganisms would clearly undermine the intent of the scoring/prioritization process and render the list impractical. Therefore, the break-point for listing a preliminary CCL microorganism on the CCL for the alternative approach was set at 50% of the highest overall score (14.5 out of 15 for toxigenic *E. coli*): any preliminary CCL microbe with a total score higher than 7.25 moved onto an "alternate microbial CCL3". Using the alternative approach and this break-point, 11 of the 22 preliminary CCL microbes were moved to the CCL (Table 1) prior to receiving a postscoring expert evaluation.

Postscoring Evaluation

The final step in the alternative approach was a "postscoring expert review and judgment". All five members of the microbial workgroup independently evaluated the list of scored preliminary CCL microbes and voted to include or not include the pathogens on the alternate microbial CCL3 (Table 2). A preliminary CCL contaminant was listed on the alternate microbial CCL3 if it received a simple majority (i.e., three or more) of votes for inclusion. These opinions were based largely on whether a pathogen is known or likely to occur in public water systems with a frequency that poses a public health threat, sensitivity to conventional treatment practices (primarily chlorination), and whether there would be a meaningful opportunity to improve public health if this microorganism were regulated. This final postscoring evaluation also included an uncertainty assessment to account for microorganisms that have documented adverse health effects but have limited occurrence information, perhaps due to lack of detection methodologies, although they are anticipated to occur in water.

As demonstrated by the EPA approach, not considering treatability when prioritizing microbes results in listing many pathogens for which existing treatment already removes or inactivates the pathogens, as evidenced by a lack of waterborne disease outbreaks in the U.S. attributed to these microorganisms. Not considering treatability will misdirect EPA resources and limit the evaluation of more resistant or robust pathogens that may pose a threat to public health and thus an opportunity for health risk reduction by their regulation may be missed. Therefore, the microbial workgroup unanimously judged that including microbes that are well-known to be sensitive to chlorination (*Salmonella enterica*, *Shigella* spp., and *Vibrio cholerae*) on the CCL3 is inappropriate. Despite the fact that *Salmonella* and *Shigella* continue to infrequently cause outbreaks in the U.S. (e.g., 124 cases of salmonellosis in June 1999 in Missouri due to a community well that had inadequate chlorine levels [20]), these outbreaks have been attributed to breaches in water treatment or unusual weather events. There have been no reports of outbreaks of cholera in U.S. drinking water supplies for decades; rather, food and foreign travel are responsible for most cases of cholera in the U.S. (*21*). Because regulations governing chlorination of surface and groundwater public water systems are already in place, it is not necessary to include them on the CCL3. Therefore, chlorine-sensitive *S. enterica*, *Shigella* spp., and *V. cholerae* were removed, leaving eight microbes on the alternate microbial CCL3 (indicated by bold text and footnote "*a*" in Table 2).

Comparing Approaches

Starting with the same preliminary CCL, the two approaches were in accord in their inclusion of five microbes on the draft CCL3 (Table 1). Differing from the EPA's draft CCL3, the alternative approach described in this paper ranked *Mycobacterium avium*, rotaviruses, and human enteroviruses relatively high (7th, 9th, and 11th, respectively), indicating that they should be included on the CCL3. Conversely, *Naegleria fowleri*, *Helicobacter pylori*, and *Entamoeba histolytica* ranked lower (12th, 15th, and 19th, respectively) suggesting that they should not be included on the CCL3. As discussed previously, while *Salmonella enterica*, *Shigella* spp., and *Vibrio cholerae* scored high using the alternative approach, the postscoring evaluation indicated that future regulation of these microorganisms would not provide a meaningful opportunity for public health risk reduction because they are already controlled by correctly operating treatment facilities that use disinfection. The key differences between the microbial workgroup's alternative approach and the EPA approach are summarized in Table 3.

Obviously, the number of microbes on the CCL can be changed by using a different threshold in the scoring process. For example, if the threshold is set at 70% of the highest score, only preliminary CCL microbes with an overall score $\geq$10.2 (using the alternative approach) would move to the alternate microbial CCL3 (6 microbes). If set at 45% of the highest score, the 16 microorganisms scoring $\geq$6.5 would be on the alternate CCL, including *N. fowleri*, *H. pylori*, and *A. hydrophila*. Ultimately, pragmatism must influence the number of contaminants that are to be listed on a CCL given the limited resources that are available to conduct the necessary research and the time frame stipulated in the Safe Drinking Water Act Amendments of 1996.

Concluding Remarks

The EPA has developed an approach to identify contaminants (the CCL) that are currently unregulated in drinking water and that may pose risks to public health. An overarching principle of the CCL process is that regulation of listed contaminants must present a meaningful opportunity for health risk reduction for people served by public water systems. Pathogen prioritization exercises and their implementation may have far-reaching regulatory, public health, and economic impacts. However, there is no single best approach that will guarantee that only the most relevant and significant pathogens are listed. Two approaches are discussed in this paper but other pathogen prioritization methods have also been recently developed (*22*). This paper describes a streamlined decision tree approach for developing the microbial CCL that explicitly, consistently, and transparently uses appropriate data in conjunction with expert review and judgment to identify those pathogens whose potential regulation would likely lead to improvements in public health. The alternative approach—which EPA should consider using or adapting as needed in developing the final CCL3 and future CCLs—used peer-reviewed published data on waterborne disease outbreaks, pathogen occurrence in water, and health effects information to score and rank microbes. It is an expert-based process that relies on the best available data but remains pragmatic when taking into consideration the realities of implementation and the implications of pathogens being listed on the CCL. An alternate microbial CCL3 was developed listing eight microbes, five of which were in

agreement with the EPA's draft CCL3. However, there are substantial differences between the two approaches (Table 3), resulting in nine preliminary CCL microorganisms or groups of related microorganisms for which the two approaches did not concur (Table 1). Ultimately the drinking water community recognizes that a systematic approach for the development of future CCLs needs to make the best use of limited resources for maximal public health benefit.

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Supporting Information Available

Additional text, figures, and tables providing background information on the preliminary CCL pathogens, and details and comparisons of the scoring methodology and results for both approaches for select preliminary CCL microorganisms. This information is available free of charge via the Internet at http://pubs.acs.org.

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