



**Comments of the Natural Resources Defense Council on the Food and Drug Administration’s Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use**

Docket ID: FDA-2015-N-0101 (formerly FDA-1975-N-0012)

October 28, 2015

The Natural Resources Defense Council (“NRDC”) is a national, non-profit environmental organization of lawyers, scientists, and other professionals. NRDC presents these comments on behalf of our 1.4 million members and online activists. NRDC does not have any financial interest in the topic of these comments.

NRDC appreciates the opportunity to comment on the Tentative Final Monograph (“TFM”) for topical antimicrobial products in health care settings. Our comments focus on the following recommendations:

1. When performing the benefit analysis for the effectiveness of chemicals in the TFM, the Food and Drug Administration (“FDA”) must properly account for a wider range of health benefits (e.g., decreases in endpoints such as asthma, decreases in antibiotic resistance) from decreased antiseptic use at the population level.
2. To show effectiveness, FDA should require that the antibacterial handwash provide a benefit of log reductions over and above washing with non-antibacterial soap.
3. To fully assess the safety of TFM chemicals, the agency must consider the impacts on populations in critical windows of susceptibility (e.g., pregnancy, childhood, elderly), particularly for chronic or highly impactful (e.g., first few days of life) exposures.
4. FDA should consider expanded health impacts (e.g., impacts to the microbiome) and clinically-relevant effectiveness (e.g., bacterial reductions in microbial communities typically found in a hospital or health-care setting) endpoints when making generally recognized as safe (“GRAS”) and generally recognized as effective (“GRAE”) determinations, respectively.

**When performing a benefit analysis for the effectiveness of chemicals in the TFM, the FDA must properly account for a wider range of health benefits from decreased antiseptic use at the population level.**

The Economic Analysis Trivializes the Impact of Healthcare Antiseptics on Bacterial Resistance

In the *Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis* (hereinafter referred to as “Economic Analysis”), FDA claims that “...we expect that bacteria in the health care setting will be exposed to multiple sources of antimicrobials – regardless of the use of health care antiseptics – which may lessen the impact of the role of health care antiseptics in the development of bacterial resistance.”<sup>1</sup>

This statement is false and represents a misunderstanding of the basic science of bacterial resistance. According to the National Institute of Health, “The use of antimicrobials, even when used appropriately, creates a selective pressure for resistant organisms.”<sup>2</sup> Several studies have found that the use of antiseptics such as quaternary ammonium and triclosan contribute to the selection and persistence of antibiotic resistant bacteria in healthcare settings.<sup>3</sup>

Therefore, lessening any use of an antiseptic will reduce the development of bacterial resistance. The FDA is discounting the overall benefit to stemming the growing reservoir of antibiotic resistant bacteria. Every year, antibiotic resistant bacteria illnesses cost the U.S. \$55 to 70 billion in economic impact, including extended hospital stays and lost productivity.<sup>4</sup> Conservatively, 2 million people are sickened by antibiotic resistant infections and 23,000 people die of those illnesses every year.<sup>5</sup> The White House has identified antibiotic resistant bacteria as a national

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<sup>1</sup> Food and Drug Administration, *Safety and Effectiveness for Health Care Antiseptics: Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, Unfunded Mandates Reform Act Analysis*, 25.

<sup>2</sup> National Institute of Allergy and Infectious Diseases, *Antimicrobial (Drug) Resistance Causes* available at, <<http://www.niaid.nih.gov/topics/antimicrobialresistance/understanding/pages/causes.aspx>>, accessed October 8, 2015.

<sup>3</sup> Chuanchuen, R., Beinlich, K., Hoang, T. T., Becher, A., Karkhoff-Schweizer, R. R., & Schweizer, H. P. (2001). Cross-resistance between triclosan and antibiotics in *Pseudomonas aeruginosa* is mediated by multidrug efflux pumps: exposure of a susceptible mutant strain to triclosan selects nfxB mutants overexpressing MexCD-OprJ. *Antimicrobial Agents and Chemotherapy*, 45(2), 428–32.

Russell, A. D. (2002). Introduction of biocides into clinical practice and the impact on antibiotic-resistant bacteria. *Journal of Applied Microbiology*, 92 Suppl, 121S–35S.

Suller, M. T. E. (2000). Triclosan and antibiotic resistance in *Staphylococcus aureus*. *Journal of Antimicrobial Chemotherapy*, 46(1), 11–18. <http://doi.org/10.1093/jac/46.1.11>

<sup>4</sup> President’s Council of Advisors on Science and Technology, *Report to the President on Combating Antibiotic Resistance*, September 2014 available at [https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast\\_carb\\_report\\_sept2014.pdf](https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf), last accessed October 27, 2015.

<sup>5</sup> Centers for Disease Control and Prevention, *Antibiotic Resistant Threats in the United States, 2013*, available at <http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>, last accessed October 27, 2015, p 6.

security concern.<sup>6</sup> Any reduction in the use of antiseptics will slow the development of antibiotic resistant bacteria. Slowing the development of antibiotic resistant bacteria confers a significant benefit that needs to be quantified by the FDA.

The FDA must also consider in this analysis the effectiveness of these antiseptics on the antibiotic resistant bacteria that cause 50 to 70% of health care acquired infections.<sup>7</sup> Reduction of bacterial load alone may not improve infection rates at hospitals if it does not tackle the problematic bacteria. Therefore, the effectiveness determination should consider the type of bacteria being reduced.

### The Economic Analysis Minimizes Benefits Due to Lack of Data

Although the FDA notes in the Economic Analysis that there are significant health benefits from removing non-GRAS/GRAE chemicals from the monograph, it wrongly dismisses the economic benefits of these health benefits for lack of data. In addition to the benefits from lessening bacterial resistance, the Economic Analysis quickly dismisses the adverse health effects that are potentially associated with exposure to non-GRAS/GRAE antiseptic active ingredients. In even trying to conduct an intermediate analysis of the reduction in exposure to these active ingredients, the Economic Analysis merely calculates the milliliters of reduced exposure that will occur.

The Economic Analysis ignores data on the cost of these potential adverse health effects altogether. For example, as discussed in NRDC's comments on the consumer handwash monograph dated June 16, 2014, triclosan and the quaternary ammonium compounds – including benzalkonium chloride – have been associated with asthma. Each day, nine Americans die from asthma. There are more than 3,600 deaths due to asthma each year, many of which are avoidable with proper treatment and care. One study has estimated the cost of pediatric asthma to be \$2 billion.<sup>8</sup> Asthma, nationwide, is estimated to cost \$56 billion (including \$50.1 billion for hospital stays).<sup>9</sup>

In addition, triclosan has been associated with endocrine disruption which can cause IQ loss in infants and young children. It is estimated that loss of IQ from lead poisoning costs \$43.4 billion

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<sup>6</sup> White House *National Strategy for Combating Antibiotic Resistant Bacteria*, 2014 available at [https://www.whitehouse.gov/sites/default/files/docs/carb\\_national\\_strategy.pdf](https://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf), last accessed October 27, 2015, p1.

<sup>7</sup> Mauldin, P. D., Salgado, C. D., Hansen, I. S., Durup, D. T., & Bosso, J. A. (2010). Attributable hospital cost and length of stay associated with health care-associated infections caused by antibiotic-resistant gram-negative bacteria. *Antimicrobial Agents and Chemotherapy*, 54(1), 109–115. <http://doi.org/10.1128/AAC.01041-09>

<sup>8</sup> Landrigan PJ et al. (2002). Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environmental Health Perspectives*, 110(7):721–728.

<sup>9</sup> Centers for Disease Control and Prevention. *Asthma Facts: CDC's National Asthma Control Program Grantees*. July 2013, available at [http://www.cdc.gov/asthma/pdfs/asthma\\_facts\\_program\\_grantees.pdf](http://www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf), last accessed October 26, 2015.

and \$9.2 billion for lead-related neurobehavioral disorders.<sup>10</sup> Presumably, a similar loss of IQ from other neurodevelopmental toxicants, including triclosan, would be similar.

Furthermore, there are new clinical trial antibiotics that are being developed, and studies have shown that triclosan use could lead to cross resistance to these drugs that have not even made it to market.<sup>11</sup> The FDA should also consider the economic benefit of allowing drugs that are being developed into the market, and not letting these antiseptics render them useless.

At a minimum, the economic analysis should allocate some portion of economic cost to the use of these chemicals that lead to these types of outcomes. A percentage of the estimated total hundreds of billions of dollars associated with these outcomes, and FDA should consider that amount in its Economic Analysis. Instead, the FDA simply dismisses the lack of specific data and significantly underestimates the benefits accrued by eliminating non-GRAS/GRAE active ingredients from the TFM.

**To show effectiveness, FDA should require that the antibacterial handwashes provide a benefit of log reductions over and above washing with non-antibacterial soap.**

On the recommendation of its Nonprescription Drug Advisory Committee, the FDA required that for over-the-counter consumer antiseptics clinical studies should be used “to show a benefit of consumer antiseptic washes over and above washing with nonantibacterial [sic] soap.”<sup>12</sup> FDA should similarly show that there is a benefit to using GRAE/GRAS chemicals in antiseptic products in the healthcare setting “over and above” washing with non-antibacterial soap. There are numerous safety concerns with many of the chemicals in this TFM, including those raised in NRDC’s comments dated June 16, 2014 and rebuttal comments dated February 15, 2015 (incorporated by reference herein). Given these concerns and given healthcare workers’ extensive exposure to these chemicals in their workplace on a daily basis, to find these chemicals GRAE, the FDA must find that there is a benefit over and above washing with plain soap and water.

A review of studies by Aiello found that, “soaps containing triclosan within the range of concentrations commonly used in the community setting (0.1%-0.45% wt/vol) were no more effective than plain soap at ... reducing bacterial levels on the hands.” In studies that did report a

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<sup>10</sup> Landrigan PJ et al. (2002). Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environmental Health Perspectives*, 110(7):721–728.

<sup>11</sup> The Pew Charitable Trusts. Antibiotics Currently in Clinical Development available at <http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development> last accessed October 26, 2015.

Grandgirard D et al. Mutations upstream of *fabI* in triclosan resistant *Staphylococcus aureus* strains are associated with elevated *fabI* gene expression. *BMC Genomics* 2015, 16:345.

<sup>12</sup> 78 Fed. Reg. 76444, 76450 (December 17, 2013).

significant benefit from triclosan soaps, the soap contained relatively high concentrations of triclosan. One study examined triclosan at 0.3% and found a significant reduction in bacterial counts “observed only after 18 hand washes per day, for 30 s[econds] each, over 5 consecutive days.”<sup>13</sup> In that study, there was no significant reduction after 1 day of use at 6 hand washes per day, 1 day of use at 18 hand washes per day, and 5 days of use at 6 hand washes per day.<sup>14</sup>

If FDA does rely on bacterial reduction as a proxy for effectiveness for the healthcare setting, it must require that that reduction be compared against plain soap and water. The risk that workers in healthcare workers face from exposure to these antiseptic active ingredients is at least the same as the risk faced by consumers using antibacterial soaps in non-healthcare settings. A study of healthcare workers’ exposure to triclosan showed that use of cleansers containing triclosan “represents a substantial and potentially biologically relevant source of occupational triclosan exposure.”<sup>15</sup> In fact, workers in healthcare settings likely wash their hands more frequently than do the general public and thus are exposed to higher levels of these chemicals.

**To fully assess the safety of TFM chemicals, FDA must consider the impacts on populations in critical windows of susceptibility, particularly for chronic or highly impactful exposures.**

As acknowledged by the TFM, health care practitioners can be exposed to antiseptics in hand washes, surgical scrubs, and other pre-operative agents during long-term, often daily, use. Health care workers represent a spectrum of the adult population, and include women and men of childbearing age, pregnant women, populations with pre-existing medical conditions (e.g., immune- and endocrine-related disorders, and practitioners of advanced age. While the TFM acknowledges the importance of developmental and reproductive studies, especially those that are propagated through the hormone balance in the body, safety for sensitive groups outside of those that are pregnant is lacking and should be considered when writing the final monograph.

In addition to vulnerable populations within the health care workforce, there is a wide variability in responses to drug exposures within the general population, as well as vulnerable individuals including children and infants, people with varied health and nutritional status, and exposure to non-chemical stressors such as economic or social stress.<sup>16</sup> The ability of the safety standards to protect populations that could experience increased adversity upon exposure to antiseptic agents should be incorporated into the recommendations of the final monograph.

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<sup>13</sup> Aiello, AE, Lason, EL, Levy, SB. Consumer Antibacterial Soaps: Effective or Just Risky? *Clinical Infectious Diseases*. 2007; 45, S137-47, 45.

<sup>14</sup> *Id.*

<sup>15</sup> MacIsaac, JK, et al. Health Care Worker Exposures to the Antibacterial Agent Triclosan. *Journal of Occupational & Environmental Medicine* 2014; 56, 834-839.

<sup>16</sup> Zeise, L., Bois, F. Y., Chiu, W. A., Hattis, D., Rusyn, I., & Guyton, K. Z. (2012). Addressing Human Variability in Next-Generation Human Health Risk Assessments of Environmental Chemicals. *Environmental Health Perspectives*, 121(1), 23–31.

Finally, as highlighted in the TFM, there are numerous populations that can become chronically exposed to antiseptic agents due to frequent interactions with the health care system or heightened use of antiseptics for the abatement/control of disease states (e.g., insulin-dependent diabetes).<sup>17</sup> Populations that have existing alternations to the functioning of their hormone systems must be adequately accounted for in the evaluation of safety. This includes the proper incorporation of metabolic parameters for disease states into pharmacokinetic models for chemical absorption, distribution, metabolism, and excretion (“ADME”).<sup>18</sup>

**FDA should consider expanded health impacts and clinically-relevant effectiveness endpoints when making GRAS and GRAE determinations, respectively.**

Safety

In addition to the evaluation of carcinogenicity, developmental toxicity, reproductive toxicity, hormonal effects, animal pharmacokinetic ADME, and human pharmacokinetics, the impacts of antiseptics on the microbiome should be more thoroughly considered in the TFM process. The human body is comprised largely of bacterial cells.<sup>19</sup> Emerging research suggests that the microbiome is essential to a wide range of physiological functions within the human system, including our immune response. Additional research suggests that alterations that occur to the microbiome early in life may result in permanent changes within the body.<sup>20</sup> Dr. Ellen Silbergeld, Professor at Johns Hopkins University has presented to the National Academies on the importance of considering the microbiome in the context of microbial resistance and human health.<sup>21</sup> It is, therefore, of utmost importance that FDA takes into account the potential impacts of the TFM chemicals on the microbiome and incorporates the downstream health effects into its benefit-to-risk calculation.

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<sup>17</sup> Tentative Final Monograph at 25169.

<sup>18</sup> Bois, F. Y., Jamei, M., & Clewell, H. J. (2010). PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. *Toxicology*, 278(3), 256–67.

Ginsberg, G., Guyton, K., Johns, D., Schimek, J., Angle, K., & Sonawane, B. (2010). Genetic polymorphism in metabolism and host defense enzymes: implications for human health risk assessment. *Critical Reviews in Toxicology*, 40(7), 575–619.

<sup>19</sup> Turnbaugh, P. J., Ley, R. E., Hamady, M., Fraser-Liggett, C. M., Knight, R., & Gordon, J. I. (2007). The human microbiome project. *Nature*, 449(7164), 804–10.

<sup>20</sup> Ajslev, T. A., Andersen, C. S., Gamborg, M., Sørensen, T. I. A., & Jess, T. (2011). Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *International Journal of Obesity* (2005), 35(4), 522–9.

Hviid, A., Svanström, H., & Frisch, M. (2011). Antibiotic use and inflammatory bowel diseases in childhood. *Gut*, 60(1), 49–54.

<sup>21</sup> Silbergeld EK. 2011. Emerging science for environmental health sciences: the microbiome. <http://nas-sites.org/emergingscience/files/2011/05/Silbergeld.pdf>

## Effectiveness

In the present TFM, FDA states that “adequate and well-designed clinical trials” that definitively demonstrate the ability of antiseptics, especially the hand washes, to reduce illness in clinically-relevant situations have not been demonstrated. The agency further suggests that clinical trials would be unethical to perform in a clinical environment, due to the risks to both health care providers and patients. While we agree with this stance, the agency should evaluate natural experiments that have already occurred (e.g., hospital systems that switched away from chemical antiseptics in hand-washes – hospitals like Kaiser and Meriter in Wisconsin) when making a final monograph decision. Looking at hospitals that have made changes might help uncover benefits (or lack thereof) of chemical antiseptics in health care settings.

In lieu of clinical trials to evaluate the effectiveness of TFM antiseptic chemicals on illness reduction in health care settings, the agency proposes to use “clinical simulation” studies as a proxy for clinical effectiveness. While clinical simulation studies do provide useful information about one possible route through which bacterial illnesses are passed in a health care setting, as currently designed, they do not study the complex microflora of the hospital environment.

Hospitals are home to a wide range of bacterial populations, yet the bacterial reduction studies required by the agency do not properly account for this. The bactericidal effectiveness of the TFM chemicals is only partially achieved in the *in vitro* testing battery; expanded protections could occur.

The 1994 TFM proposed that for a chemical to obtain a GRAE determination, minimum inhibitory concentration (“MIC”) testing had to be performed on 25 fresh clinical isolates and 25 laboratory strains, and time-kill testing against 23 laboratory strains.<sup>22</sup> The expansion of the present TFM to include these testing requirements, despite previous commenters finding the rules burdensome, is well-founded. In addition to the proposed isolation strains, however, the *in vitro* tests could mirror the “worst-case” real-world assumptions in the maximal usage trial (MUsT) studies. Clinical isolates that closely represent worst-case hospital or health care microbial populations (e.g., large numbers of multi-drug resistant bacterial strains) could be highly useful in determining the effectiveness of a chemical under real-world conditions. Worst-case assumptions could include patient-derived isolates from cases involving isolation due to multi-drug resistance or isolates from frequently contaminated surfaces within a hospital or health care setting (e.g., door knobs, soap dispensers, etc).

This type of testing could be expanded into “clinical simulation” studies by measuring log reduction of bacterial counts on hands contaminated under actual health care conditions. Bacterial samples taken from the skin (e.g., the hands) could be taken before a clinical task is performed (e.g., changing soiled garments), after the task, and following the use of the antiseptic

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<sup>22</sup> Tentative Final Monograph at 25177.

agent. This process would account for the variability that can occur in the number of bacteria present on the skin of the health care worker. This process, or something similar, would allow for the evaluation of antiseptic products in the situations that are potentially more relevant in a health care setting.

## **Conclusion**

As FDA explained in its proposed TFM, there are insufficient data regarding the safety and efficacy of many of the healthcare topical antiseptics active ingredients. These chemicals raise significant concerns with respect to hormone disruption, antibiotic resistance, and other adverse health impacts. In addition, if FDA determines that bacterial log reduction is the appropriate basis to show effectiveness, than that log reduction should be greater than the reduction from using non-antibacterial soap. FDA must expand its consideration of health impacts and of vulnerable populations. The healthcare professionals and other workers in the healthcare setting must be equally protected from the potentially adverse health effects associated with these chemicals.

Thank you for the opportunity to provide these comments.

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