DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

NON-PRESCRIPTION DRUGS

ADVISORY COMMITTEE

Thursday, October 20, 2005

8:00 a.m.

Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

Alastair Wood, M.D., Ph.D.,Chair
LT Darrell Lyons, BSN, Executive Secretary

MEMBERS

Terrence F. Blaschke, M.D.
Ernest B. Clyburn, M.D.
Jack E. Fincham, Ph.D.
Ruth M. Parker, M.D.
Wayne R. Snodgrass, M.D., Ph.D.
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Mary E. Tinetti, M.D.

CONSULTANTS (VOTING)

Matthew J. Arduino, M.S., Dr.Ph
Rolf Halden, Ph.D.
James Omel, M.D., (Patient Representative)
Sonia Patten, Ph.D. (Consumer Representative)

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Mark A. Hartman
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Charles Ganley, M.D.
Susan S. Johnson, Ph.D.
Debbie Lumpkins
Steven Osborne, M.D.
John Powers, M.D.
Colleen Rogers, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. WOOD: Good morning. I would like to call the meeting of the Nonprescription Drugs Advisory Committee to order.

Lieutenant Darrell Lyons will read the Conflict of Interest Statement.

Conflict of Interest Statement

LT LYONS: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted to the

following participants because they have interests in firms that could potentially be affected by the committee's discussions.

Dr. Ruth Parker has been granted a waiver for serving as one of the co-editors of a special issue of the Journal of General Internal Medicine on health literacy. Dr. Parker will receive less than $5,000 from one of the affected firms for serving as co-editor.

Dr. Sonia Patten has been granted a waiver because she is an unpaid volunteer member of the Sumsail Foundation Board of Directors and the Foundation owns stock in one of the affected firms, worth between $25,001 to $50,000.

We would also like to disclose that Dr. Stuart Levy has received a limited waiver because he is the Vice Chairman of the Board of Directors, Chief Scientific Officer, and co-founder of a firm that could be affected by the committee's discussions. Under the terms of this limited waiver, Dr. Levy will be permitted to give a presentation on the antimicrobial use and the

potential for the development of resistance and answer questions directly related to his presentation. Dr. Levy is excluded from participating in any of the committee's discussions, deliberations, or voting.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Officer, Room 12A-30 of the Parklawn Building.

We would also like to disclose that Dr. James Omel and Dr. Terrence Blaschke own stock in firms that could be affected by the committee's discussions. Because these stock interests do not exceed $25,000 in any one affected entity or $50,000 in all affected entities, 5 CFR Part 2640.202(b) de minimis exemption applies and a regulatory waiver under 18 U.S.C. Section 208(b)(2) covers those interests.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all participants, we ask in the interest of fairness that they address any current or previous financial involvements with any firm whose product they may wish to comment upon.

The Industry Representative for the NDAC Committee recently resigned. That position being currently vacant, the Center contacted and invited an Industry Representative who is currently a member of a different CDER Advisory Committee to participate in today's meeting. This representative had agreed to attend, however, an unexpected and last-minute emergency has prevented attendance at this meeting. Thus, for today's meeting, we do not have an Industry Representative.

Thank you.

DR. WOOD: Okay. Susan, do you want to begin? Thanks.

Welcome and Introductory Comments

DR. JOHNSON: Thank you, Dr. Wood. Good morning to our Chairperson, Committee members,

invited speakers, and guests.

My name is Susan Johnson. I am the Associate Director of the Office of Nonprescription Products and acting as the Division Director in the Nonprescription Regulation Development Division.

As we have heard in the press already, I think in particular Matt Lauer has an interest in these products. Certainly, the consumer antiseptics that we are going to be discussing today have widespread use and widespread interest, so we are looking forward to an interesting discussion.

[Slide.]

We thought it would be helpful for the committee to revisit very briefly the March 2005 meeting in which we discussed healthcare antiseptics. The topics of this meeting are different, but we thought it would be helpful to give a brief review.

The products discussed in March were surgical handscrubs, healthcare personnel handwashes, patient preoperative skin preparations, all designed to be used within the healthcare

setting and the population therein.

That is a general definition and we will be clarifying that more as the day goes on.

We discussed at length at the March meeting the benefits of the healthcare antiseptic product, and we were assuming an infection risk that was fairly large associated with the healthcare setting.

We also discussed the reduction of risk by reducing the presence of bacteria, and worked extensively at that meeting to define what appropriate effectiveness criteria should be. I think it is going to be a relief to the committee to know that we are not going to go into the effectiveness criteria with such depth this time.

We did not spend a long time at the March meeting discussing safety, and that will become a more prominent issue for the consumer antiseptics.

[Slide.]

So, the consumer antiseptic products are currently marked in a variety of categories, a variety of formulations, and a variety of active

ingredients. They exist as antibacterial soaps, antibacterial wipes, antibacterial bodywashes, and hand sanitizers.

[Slide.]

The population intended for use of the consumer antiseptics has not been clearly defined, and that is something that we are going to be asking the committee to refine for us. Our working definition are individuals outside of the healthcare setting.

NDAC is also being asked to consider today the healthcare status of those individuals varying widely from healthy adults, healthy children, to healthy people taking care of people with illnesses in the home, to people who are actually ill, living mostly outside of the healthcare setting, such as a chemotherapy patient.

We are going to be focusing on the difference between the healthcare antiseptic product population and the expected infection risk, and the difference between that risk and the infection risk for people outside of the healthcare

setting.

We are also going to be talking a little bit about where the healthcare population overlaps with the consumer population.

[Slide.]

Specifically, we are going to be asking the committee to consider benefits of consumer antiseptics, what is the purpose of them, is it to reduce the risk of infection? Do individuals outside of the healthcare system require routine use of these products? How does the use of these products compare to other hygiene methods, such as washing hands with plain soap and water?

[Slide.]

As I said earlier, the hazards are going to become more prominent for the consumer antiseptic discussion. We are going to be focusing on risks to the individual, such as local, short-term risks, and more long-term systemic risks, which you will hear about in more detail later.

We will also be talking about a category

of risk that is not normally considered or not usually considered, is not part of a discussion at an advisory committee, but we are going to touching on potential societal risks associated with the consumer antiseptics.

DR. WOOD: Thanks a lot.

Before we move on to the next speaker, let's just cover a couple of housekeeping things. First of all, can I ask everybody to turn off their cell phones, so that we don't have them going off during the meeting, if we can.

Secondly, I had hoped that, in fact, somebody just has arrived, that the blanks in the committee would be filled in before we got to this point, so perhaps we could go around and introduce everybody who is around the table.

We will start with you, Charley.

DR. GANLEY: I am Charley Ganley. I am the Director of the Office of Nonprescription Products.

DR. JOHNSON: Susan Johnson, Associate Director, ONP.

MS. LUMPKINS: Debbie Lumpkins. I am a team leader in ONP.

DR. ROGERS: Colleen Rogers. I am a

microbiologist in ONP.

DR. OSBORNE: Steve Osborne. I am a medical officer in ONP.

DR. OMEL: Jim Omel. I am a Patient Representative.

DR. ARDUINO: Matt Arduino. I am a Lead Microbiologist in the Environmental and Applied Microbiology Laboratory at the Division of Healthcare Quality Promotion at CDC.

LT LYONS: Darrell Lyons. I am the Executive Secretary for the committee.

DR. WOOD: I am Alastair Wood from Vanderbilt.

DR. BLASCHKE: Terry Blaschke from Stanford.

DR. FINCHAM: Jack Fincham, the University of Georgia.

DR. SNODGRASS: Wayne Snodgrass, University of Texas.

DR. TINETTI: Mary Tinetti, Yale University.

DR. CLYBURN: Ben Clyburn, Medical University of South Carolina.

DR. TAYLOR: Robert Taylor, Howard University.

DR. PATTEN: Sonia Patten. I am the Consumer Representative. I am from Macalester College in St. Paul, Minnesota.

MR. HARTMAN: I am Mark Hartman, Branch Chief at the Office of Pesticide Programs in EPA.

DR. WOOD: Let's move on then to the next speaker who is Colleen Rogers.

Regulatory History and Attributes of Consumer Antiseptic Drug Products

DR. ROGERS: Good morning. As you have just heard, I am Colleen Rogers, a microbiologist in the Office of Nonprescription Products. Today, I will be giving you a brief overview of the regulatory history of consumer antiseptics.

[Slide.]

For my talk today, first, I will give a

brief overview of the monograph process. Then, I will describe how consumer antiseptics have been defined both by FDA and industry over the years to give you a sense of how this process has evolved.

Next, I will describe some of the attributes that these products may have, and I will also mention some of the concerns that have been raised during the evaluation of these products.

[Slide.]

The monograph system is a three-phase public rulemaking process. This results in the establishment of standards or monographs for every over-the-counter therapeutic drug category.

Beginning in 1972, an initial drug review was undertaken by an Advisory Review Panel composed of scientific experts from outside of FDA. This review panel evaluated the safety and effectiveness of a list of active ingredients for each OTC drug class.

They then put each ingredient into one of three categories. Category I is Generally Recognized As Safe and Effective. Category II is

Not Generally Recognized As Safe and Effective.

For Category III, there was not enough information to determine whether the ingredient was safe, effective, or both.

[Slide.]

FDA then uses the recommendations of the panel to draft a proposed rule. The proposal is published in the Federal Register as an Advance Notice of Proposed Rulemaking or ANPR.

[Slide.]

After the ANPR is published, we consider public comments as we develop a tentative final monograph or TFM. The TFM is FDA's proposed monograph.

[Slide.]

The last step in the monograph process is to again seek public comment and additional data regarding the safety and effectiveness of ingredients. This information is used to formulate the final rule or final monograph, shown here as FM. I would just like to point out that manufacturers are not required to comply with the

regulations until the final rule is published.

[Slide.]

Here, I have listed a summary of the steps in the development of the antiseptic monograph. The recommendations of the review panel were used to draft the Advance Notice of Proposed Rulemaking in 1974.

Then, in addition to comments from the public, the proposed rule was drafted and published in 1978, and this is the first TFM, but I would also like to point out that the TFM was amended in 1994, and when I refer to the TFM later in my talk, I am referring to this 1994 TFM.

[Slide.]

I would like to start with just a basic definition of an antiseptic. An antiseptic is a product that contains an antimicrobial ingredient that is nontoxic enough to be used on the skin. These are considered drugs and therefore regulated by FDA.

A disinfectant also contains antimicrobial ingredients, but these are used on inanimate

objects and surfaces. Even if these products contain the same active ingredients as an antiseptic, they are regulated by the Environmental Protection Agency. You will hear more about EPA's regulatory process for antimicrobials later this morning.

[Slide.]

Currently, there are a wide variety of consumer products available. As Sue Johnson mentioned earlier, these are currently marketed as liquid, solid, or foam antibacterial soaps, antibacterial wipes and towelettes, antibacterial bodywashes, and a variety of waterless or leave-on products, such as alcohol and alcohol-free hand sanitizers.

[Slide.]

We have broadly divided the antiseptics into three categories based on their target users. As you know, we have discussed the healthcare antiseptics back in March, and food handler antiseptics will be handled at a later date, so today, we are focusing just on products used by the

general population outside of the healthcare setting.

Historically, FDA defined consumer antiseptic as "antimicrobial soap." The Advisory Review Panel defined this as a product that reduces the microbial flora of the skin. They also recognized that these products may reduce both resident and transient organisms.

The proposed use of antimicrobial soap was not limited to the hands, and the target users were not identified.

Then, in the 1978 TFM, FDA further defined antimicrobial soap, and they were distinguished from healthcare personnel handwashes. FDA felt that these products should be intended for the general public in only non-hospital settings.

Then, in 1994, the term "antimicrobial soap" was replaced with "antiseptic handwash." An antiseptic handwash is defined as a product used by consumers on a frequent, even daily basis, and includes products for personal use in the home, such as when caring for invalids or during family

illness.

This category of products includes both rinse-off products and waterless or leave-on products, and it does not encompass products used for areas of the body other than the hands.

[Slide.]

The proposed labeling claims also have changed over the years. Initially, consumer products could be called antimicrobial or antibacterial soaps, but most often they were marketed as deodorant soap with a claim of reduces odor.

When the consumer category was further defined in 1978, FDA felt that the different uses required different labeling for consumers and healthcare personnel. Furthermore, there was insufficient data about the ability of these products to prevent infections to allow claims for prevention of infection.

[Slide.]

Then, in 1994, the labeling claims were changed to either antiseptic or antiseptic handwash

with an indication of for handwashing to decrease bacteria on the skin. Manufacturers were also allowed to add phrases, such as "after changing diapers" or "after assisting ill persons," and they also could label it as "recommended for repeated use."

In 2003, FDA received a Citizen Petition from the Soap and Detergent Association and Cosmetic, Toiletries, and Fragrance Association industry coalition. They requested antiviral claims for all categories of antiseptic products.

This request is currently under evaluation. Since this topic is broad in scope and applies to more than just the consumer products, we are not going to address it today, but we are just going to focus on antibacterial claims.

[Slide.]

Only one category was proposed in the 1994 TFM for consumers, and this is the antiseptic handwash. The regulated industry felt that the antiseptic handwash category did not encompass all of the relevant products.

So, in 1995, they submitted a proposal to FDA called the Healthcare Continuum Model. In it, they proposed 6 categories of antiseptics including

2 for consumers, an antiseptic handwash and an antiseptic bodywash.

[Slide.]

The active ingredients used to formulate consumer antiseptics overlap quite a bit with those used in the healthcare antiseptics. These include ethanol, which can be found, for instance, in purol hand sanitizer; triclosan, which is a very common ingredient in liquid antibacterial soaps, such as Dial; triclocarban, which is found in bar soaps, such as Safeguard; and quaternary ammonium compounds, benzalkonium and benzethonium chloride. These compounds are often found in antibacterial wipes.

[Slide.]

As I mentioned, the consumer products are covered under the antiseptic handwash category in the TFM and, as such, FDA has considered the attributes of consumer products to be the same as

for healthcare products.

For the purpose of my talk, antiseptic handwashes, wipes, and sanitizers will be considered collectively as antiseptic handwash.

According to the TFM proposal, antiseptic handwashes should be broad spectrum, fast-acting, and, if possible, persistent.

Fast-acting refers to a product's ability to reduce bacteria on the hands within the amount of time in the testing requirements, which is 10 minutes.

Persistent refers to the ability of an antiseptic to remain on the skin after a single application.

The TFM does not distinguish between consumer products and healthcare products when it comes to efficacy testing. Antiseptic handwashes should achieve a specific bacterial log reduction after 1 and 10 consecutive washes, and this demonstrates the cumulative or additive effect.

[Slide.]

The industry coalition provided proposed

attributes and efficacy testing in their Healthcare Continuum Model. Similar to FDA's proposal, industry suggests that consumer antiseptics should be broad spectrum and persistent, however, they suggest fact-acting is not an essential attribute.

The coalition proposed a single wash to demonstrate efficacy rather than multiple washes, and more recently, they have proposed that there should be no requirement for a cumulative effect.

[Slide.]

The Healthcare Continuum Model also provides proposed efficacy testing and attributes for antiseptic bodywashes. These products may be either limited or broad spectrum, they should be persistent, and again, fast-acting is not an essential attribute.

Industry's proposed efficacy testing allows for testing either resident or transient flora using standardized test methods. In contrast, the TFM does not have any proposed attributes or efficacy testing for bodywashes since this category has not been identified in any

previous rulemakings.

[Slide.]

Like all drugs, the use of antiseptics may pose some risk to the user. The individual user may experience irritation or allergic reaction. After more extensive use, antiseptic or antibiotic resistant organisms could develop in the individual.

Another theoretical hazard to the individual is incomplete immune system education or development in the absence of stimulation by microbial antigens. It is thought that this leads to an increased incidence of allergies and asthma, and is known as the "hygiene hypothesis." However, this is still a controversial hypothesis.

In addition to risk to the individual user, several potential hazards may occur in the community due to chronic exposure of the environment to antiseptics. This may include widespread development of antibiotic resistance, a negative impact on ecosystems, and secondary exposure to humans. You will hear more about these

later today.

[Slide.]

The data evaluated by the Advisory Review Panel in 1972 caused it to voice a hypothetical concern that routine use of antimicrobial soaps may have a long-term harmful effect by reducing the protective effect of the normal flora.

If this were true, certain bacterial infections from gram-negative organisms might be increased. The panel went on to say that if the hypothesis was true, the deodorant benefit would be outweighed by the potential hazard.

The panel also expressed concern that the widespread use of anti-gram-positive antibiotics, antiseptics, and hard-surface disinfectants, which are often effective against gram-positive organisms, may produce an increase in gram-negative infections in hospitals and other closed environments.

Finally, the panel also expressed a concern that since these chemicals are absorbed through the bloodstream, it might not be prudent to

expose the entire body to them when other methods of odor control are available.

[Slide.]

In the 1978 TFM, FDA stated its concern about the proliferation of triclosan-containing products. They concluded that if the number of sources of these ingredients appeared dangerously high, the availability of these products should be curtailed. This was especially true for bar soaps.

But in 1994, based on new information, FDA concluded that proliferation of triclosan-containing products was not a concern.

FDA has been concerned about the development of antibiotic resistance as a result of antiseptic use. We brought this issue to NDAC in 1997. At that time, NDAC felt that decreased susceptibility to antiseptics and the development of antibiotic resistance was not a concern. However, they stated that ongoing surveillance for the possible development of resistance to these agents was prudent.

[Slide.]

FDA continues to be concerned about the development of antibiotic resistance as a result of antiseptic use. It has been nearly nine years

since we brought this topic to NDAC's attention, and in that time, there has been a lot of literature published on the subject.

So, based on this new information, we would like to know if this may present a concern for us today. Furthermore, based on the widespread use of these consumer products, we are re-examining the risks to the consumer.

This includes environmental concerns, such as secondary exposure to human and negative impact on ecosystems.

Finally, as a follow-up to the March NDAC meeting on professional use products, we would like to define the attributes of the consumer products.

[Slide.]

As I already mentioned, we are in the process of finalizing the monograph, and to do this we will need to develop some policies, and we need your input today to help us to do that.

The main questions that we need answers for today are: What population would benefit from the use of consumer antiseptics? How do we measure the benefit of these products? What potential hazards, if any, should we take into consideration during our decisions about product regulation?

Now, I would like to introduce Dr. Steven Osborne, who will be talking about the clinical benefit of consumer antiseptics.

Clinical Benefit of Consumer Antiseptics

DR. OSBORNE: I am Steve Osborne. Thank you, Dr. Rogers, Dr. Wood, members of the Committee, industry representatives, and interested public. I am going to speak today about the clinical benefit of consumer antiseptics.

[Slide.]

First, looking at the question, does the clinical evidence link use of consumer antiseptics with clinical benefit meaning a reduction in infection risk.

[Slide.]

We will examine data from the Citizen's

Petition 16, FDA's own literature search, and try to determine if there is a clinical benefit from a specific antiseptic or from a hygiene method, such handwashing alone, handwashing with or without training, handwashing with training with or without disinfectants, all different varieties.

[Slide.]

First, from the Citizen's Petition, there were 31 articles and abstracts, most of which related to professional use, which has been previously discussed at the March '05 Healthcare Antiseptic Advisory Committee Meeting.

Twenty-five of these articles had a weight of evidence that was not persuasive for clinical benefit of consumer antiseptics. Two looked at a microbial risk assessment model, two described other models, these weren't pertinent. Two looked at hand sanitizer use in schools, and we will discuss these a little bit. Guinan et al. and Dyer et al.

Overall, though, there was no link between use of any particular antiseptic and a reduction in

infection rates.

[Slide.]

Summary of the study limitations that might have applied to these references, not every reference had every limitation, but all of them had at least one.

They were not designed to assess a contribution of an active ingredient to the infectiveness of the product, the product being the whole program that was being used.

Not designed to assess a single ingredient effectiveness versus simply hand hygiene alone, meaning washing basically with soap and water.

Lack of standardization of product use. You might not have explained how often people were to wash, or if you did, how long they were to wash. There is a difference between washing for 10 seconds and washing for 5 or 10 minutes in terms of removing at least transient bacteria.

There might have been a lack of standardization of product use, as I mentioned, and bacterial transfer studies were not correlated with

a clinical outcome.

So, these references might be applicable to a healthcare setting and not to a consumer use setting.

[Slide.]

Looking first at two handwash studies, and then later at four hand sanitizer studies, the FDA did a literature search and found two handwash studies I would like to review with you.

Larson et al. 2004 looked at antibacterial ingredients in the home versus infection symptoms.

Luby et al. 2005 looked at handwashing plus bathing versus respiratory infection, diarrhea, and impetigo.

[Slide.]

First, Larson et al. 2004. For each of the 6 studies that I am going to look at, I will look at the design, compare the test and the control group, look at the primary endpoint or endpoints of the study, the results, and a study interpretation.

Larson's was a 48-week, randomized,

double-blind, placebo-controlled study of 224 households in inner city New York with at least 3 people in the household, 1 of whom was in preschool.

Investigators made weekly calls, monthly and quarterly visits. They used a 31-page validated form for home hygiene practices and illness data. This particular design allowed them to publish a half-dozen articles involving this study, of which I am simply going to go over what I think is the main article talking about infection rates. You may hear later about some other aspects of this study.

Ninety-three of the first 100 self-reported illnesses by the consumers in their home were verified by a visiting physician. This allowed the investigators the assurance that self-reporting seemed to be a valid measure and they no longer needed to have physician visits.

The primary endpoint was at least one infectious disease symptom within the household for each 1-month period.

[Slide.]

Comparing the test and the control group, the difference is this antimicrobial products right

here. Otherwise, they were similar. The antimicrobial products were liquid triclosan soap, which is an antiseptic, a quaternary ammonium hard surface cleaner, and an oxygenated bleach detergent, which are disinfectants, and then there was a liquid kitchen spray. It is not clear what was in that.

Both groups received a non-antimicrobial dish liquid and bar soap to use by whatever their normal practice might be.

[Slide.]

The results looking at the rate of at least one infectious disease symptom for each household. Now, if you look along the left here, you have the symptoms. These are not disease diagnoses, but simply vomiting, diarrhea, fever, sore throat, runny nose, cough, et cetera.

Looking at the rate, you have the antibacterial group and the non-antibacterial

group. Both the confidence interval for the unadjusted relative risk for that symptom in either group, antibacterial or non-antibacterial, and the adjusted relative risk, those confidence intervals include 1.0 for every number in the table. The p-values are all greater than 0.11.

[Slide.]

What this says to us is that the adjusted and unadjusted relative risks for each symptom show no advantage of antibacterial product use in reducing infections.

The authors concluded that the symptoms likely reflected viral illnesses, which makes sense. You have a cough, you have a runny nose, and typically, colds and flu are a lot more common than, for example strep throat, which could encompass some of those symptoms, but just not as commonly as viral illnesses might be.

Then, if you look at the fact that multiple antimicrobials were used, the antiseptic triclosan was combined with the disinfectants, the disinfectant hard surface cleaner, et cetera, this

would have confounded the assessment of the value of any single antiseptic. So, we cannot assess whether use of the antiseptics would reduce transmission of bacterial infections per the authors, because we looked mostly at symptoms relating to viral illnesses, and this does make sense.

[Slide.]

Luby et al. did the Karachi Soap Health Study. The design was a randomized, double-blind, placebo-controlled trial in 36 neighborhoods, encompassing 906 households, of which 300 were in the test group, 300 in the placebo group, and they had 306 in a plain control group, which helped to make this study more robust. This was done in Karachi, Pakistan.

Handwashing promotion was given to the soap neighborhoods, both the test and the placebo soap neighborhoods. School supplies were given to the control neighborhood, so that they would have something to make them interested, but nothing to affect their hygiene practice.

The soap was randomized in the intervention households to a 1.2 percent triclocarban soap, which we have heard is like

Safeguard, or a non-medicated soap. The soap was supplied free and it appeared the same for both groups.

The field workers assessed the illness and physicians corroborated any diagnosis of impetigo.

The endpoint was the incidence of acute respiratory infection, impetigo, and diarrhea.

[Slide.]

Comparing the groups, you see the difference between the three groups. Field workers visited those control and intervention groups weekly and encouraged children over 2 1/2 years old in both the test and the placebo groups, but again not the control group, to wet, lather their hands for 45 seconds, rinse them, and then dry them on their clothing, which was their practice.

They were to do this after defecating, before food prep and eating, before feeding infants, and they were also to bathe once daily

with soap.

[Slide.]

The results of this show that the mean incidence episodes per 100 person-weeks, you look at coryza, diarrhea, and impetigo, the antibacterial and plain soap group both had a significantly lower incidence of illness for each of these three disease categories versus the control group.

The 95 percent confidence interval of the difference compared with the control excluded zero. However, the antibacterial soap group and the plain soap group were not different from each other for any of these values. These are indistinguishable statistically.

[Slide.]

So, the interpretation is that handwashing plus bathing with soap reduces respiratory infection, diarrhea, and impetigo, but the reduction in the disease is simply due to handwashing plus that daily bath with soap versus simply promotion. There was no added benefit from

adding the triclocarban to the soap.

The authors concluded that the antibacterial soap did not provide a health advantage over plain soap for any of the health outcomes in their study.

[Slide.]

Limitations might be that the study personnel and participants were not masked to the soap intervention. Everybody knew who had soap even though you didn't know which kind of soap you had, but that could have had the participants underreport their symptoms to please the investigators perhaps.

Bathing and overall promotion confounds the attempt to attribute the effect to handwashing alone because of that one daily bath that they advocated.

[Slide.]

Now, turning to some hand sanitizer examples from both the Citizen's Petition and the FDA literature search, I am going to look at four articles.

Now, with hand sanitizers, generally, these are either gels or wipes. With the gel, you rub it into your hands and then just have your

hands air dry, and that's it. With the wipe, you would wipe your hands with the wipe, toss the wipe, let your hands air dry. That is how you use the hand sanitizers.

Dyer et al. 2000 looked at a reduction in school absenteeism, as did Guinan et al. in 2002. Sandora in 2005 looked at a hand sanitizer at the home versus respiratory and GI illness. Lee et al. in 2005 looked at alcohol gels at home and illness transmission.

[Slide.]

Dyer's study was a 10-week, open-label, crossover study in one school. There were 420 students ages 5 to 12, grouped by class, about 30 in a class, 7 classes in both groups. There was no randomization, and this was unblinded.

Every person in the class was either in the test group or in the control group. Within the class, there was no randomization. Everybody was

in one group or the other.

The illnesses were GI or respiratory, and the parents decided why their student was absent that day.

The test sanitizer was called an SAB, which is a surfactant plus benzalkonium chloride.

The endpoint, the incidence of illness absenteeism.

[Slide.]

All students had a 30-minute talk on germs and handwashing, and they were shown a video. They were told to wash with non-medicated soap before eating and after using the bathroom.

The other difference between the test group was simply that the test group would sanitize upon entering the class, after sneezing or coughing, and they were to rub a quarter ml of this SAB into their hands, and specifically their fingertips and nails were to be touched until they were dry.

They were monitored. The control group was not monitored.

[Slide.]

The student absence data, there was a 2-week washout in between the first 4 weeks and the

second 4 weeks, showed that in the control group, there were 105 days of illness and only 70 in the sanitizer. That was significantly different.

Similarly, in the second 4-week period, there were 63 days of illness in the control group, 28 in the sanitizer group. That was significantly different, as well.

[Slide.]

Now, a limitation of this study or set of limitations might be that it was clustered. In other words, all 30 had one intervention, and so you get one infection in that classroom, it can spread like fire and perhaps bias the results.

There was no placebo. The control group did not have a bland pump spray. The study was unblinded. There was no specified length of time for the wash, and I think we all know that how long you wash can affect how many bacteria you knock off your hands or kill on your hands.

The test group was monitored, but not the control, and the test group was advised to wash more often. They were told to sanitize upon entering the classroom and the other times that were shown.

It was a single site.

The question that arises, are these illness rate differences due to monitoring and the number of times washing, and not simply due to the hand sanitizer.

[Slide.]

Guinan et al. was a 3-month, open-label, 5 private school study. There were 290 students, grades K to 3, grouped by class, 9 classes in the test and the control group. There was no randomization, it was unblinded.

The teachers collected the data on the illness, which were cold, flu, and GI, and either the parents or the child told the teacher why they were absent from school, which of these illnesses, if any of them, might have been the reason.

The test sanitizer was an alcohol-based

instant sanitizer with aloe.

The endpoint was the incidence of illness absenteeism defined as the number of episodes of illness per child per month.

[Slide.]

All students had the 10-minute talk on handwashing, a video, and a pamphlet, but no demonstration on how to wash.

The test group had the sanitizer. They also got a handwashing demo, and then the students were tested to make sure that they understood how to wash. Neither group was monitored.

[Slide.]

There were 277 episodes of absenteeism in the control group, 140 in the test group. The lower absenteeism in 23 of the 27 months in the test group was significant.

There were 50.6 percent fewer episodes of absenteeism in the test group. That was significant.

[Slide.]

The authors concluded a successful

handwash program included: administrative support, you have got to have the teachers and the school behind it; a 1-hour hand hygiene in-service, and the use of hand sanitizers in the classrooms and in the bathrooms.

[Slide.]

Limitations. There were no comparisons to plain soap. It was not randomized, it was unblinded. There was a homogeneous population, upper-middle class. Home variables were not assessed. You know, these students would go home, and you don't know what their sibling at home might have had in terms of illness, and was there smoking at home, for example, what healthcare visits were made at home.

The student's actual handwashing and sanitizing was not observed, tallied, or assessed. The test group received handwashing training. Now, the authors note that a similar study showed that when you give the control group handwash training, there was only a 19.8 percent lower absenteeism in the control group given the handwashing training.

There was 50.6 percent in this study. That might suggest that the training itself has a significant effect.

[Slide.]

Sandora et al. in 2005. There is a 5-month, randomized, open-label, controlled trial, 292 families, 1 child age 0.5 to 5 years old in day care. Twenty-six child care centers were randomized, and if you were using the hand sanitizer all the time, you couldn't be in the study.

The alcohol-based instant hand sanitizer was used and it had aloe. Primary outcome was the rate of secondary respiratory and GI illnesses.

Now, secondary illnesses are when some sick person goes home, how many other people get sick. That is a secondary transmitted illness. That is what they mean by that.

[Slide.]

The test and the control groups had the sanitizer versus usual practice, and everything else was the same.

[Slide.]

Looking at these results, total illnesses. Now, this is primary and secondary. In the control

group, it was 117 and the intervention, 135, and that is for GI illnesses.

Respiratory illnesses, being more common, had 828 in the control and 974 in the intervention. The incidence rate for total illnesses, not secondary and primary different, but just total, were indistinguishable between the control and the intervention group.

When you look at the secondary transmission of the illness, though, you have an incidence rate for GI illnesses in the control group of 0.35, and in the intervention group, 0.17. Now, this is not significant, 0.08, until you adjust for seven variables. After that seven-variable adjustment, the p is 0.03. We will get to that in a minute.

For the respiratory illnesses, there was no difference in the incidence rate.

[Slide.]

So, the limitations of this study are that it is not blinded, the hand sanitizer use was not monitored. The hand sanitizer was combined with education. There was no placebo sanitizer for the control group.

There was a low initial participation, 647

eligible families, only had 292 that were actually randomized.

Now, it is unclear whether this adjustment for the seven variables was pre-planned or post-hoc. The authors intended to look at the secondary transmission of illness rate, but whether this statistical thing is valid or not is not clear.

There is a clinical significance of secondary GI illness reduction of 10 versus 18, and that is also not clear whether that absolute difference of 8 illnesses out of, as we saw, there were about 1,500, whether that difference is significant or not clinically is not clear.

[Slide.]

Lee et al. 2005 was an observational--that

means no intervention--uncontrolled, prospective cohort study in families in the Boston area over 18 months. At least one child less than 5 years old had to be present and there had to be a child in daycare for 10 hours a week.

Recruitment was from 5 pediatric practices, 250 families in each practice. They analyzed the predictors of secondary transmission of illness. There is another study that is looking at the secondary transmission.

The endpoint is the rate of secondary respiratory and GI illness per susceptible person-month.

The concept might be that you may not always be able to prevent the first illness, but once you start using some hand sanitizer technique, you may be able to prevent the secondary transmission of illness.

[Slide.]

The results are that 208 of the 1250 families were available for analysis; 1545 respiratory illnesses, 1099 primary, 446 secondary,

and the GI illnesses are lower numbers.

The secondary transmission rates were 0.63 for respiratory and 0.35 for GI.

The incidence rate ratio for the secondary transmission of the respiratory illnesses was 0.6, and the p is 0.01. This is not adjusted, though, for multiple comparisons for use of the alcohol gels.

The authors also looked at other factors, such as whether you had some high school or not, and that caused a significantly lower incidence of the secondary transmission of GI illnesses.

They also looked at what insurance you had, if you had Medicaid insurance, that increased your risk for the secondary transmission of GI illnesses.

[Slide.]

So, the limitations of this study might be that it's observational, that is, no intervention. It is uncontrolled. It is not designed to assess alcohol efficacy or any other antiseptic as a primary endpoint.

They looked at many different variables related to why people got sick, including their insurance status and their education.

The p value, less than 0.05, that we saw, may not be significant. It is not clear that it's adjusted for these multiple comparisons that were made.

[Slide.]

Summary. The data from the Citizen's Petition 16 and the literature review shows: A clinical benefit from handwashing; No added benefit from triclocarban soap. We saw that in the Luby study.

No definitive proof of a benefit from use of hand sanitizers for handwashing compared to plain soap.

[Slide.]

I return to the question asked at the beginning: Does the clinical evidence link use of consumer antiseptics with clinical benefit meaning a reduction in infection rates?

I would like to introduce the next

speaker, Dr. Allison Aiello, who will speak to us also about consumer antiseptics.

Community-based Studies of Consumer Antiseptics

DR. AIELLO: Good morning. Today, I am going to be talking about a lot of the things that Steven brought up, discussing community-based studies of consumer antiseptics.

[Slide.]

What I will do is go over a literature review that we conducted. I will talk about some of the methodological issues for each of the studies that we retrieved through that literature review, and then I will give a summary of the research at this point and the future research needs.

[Slide.]

The overall goal is to estimate the reduction in risk attributed to specific hand hygiene products. The way that we set this up was we looked at the research by specific products that are available over the consumer market.

We looked at plain soap handwash, so we

can get an idea of what is the reduction in infections related to plain soap handwash, antiseptic soap handwash including triclosan and triclocarban, hand sanitizers including alcohol-based hand sanitizers, and then non-alcohol based hand sanitizers including benzalkonium chloride.

I am not going to have a lot of time to talk about those studies, and you see in a second there is only a few that have looked at those ingredients.

[Slide.]

So, what we did to retrieve articles, we used earlier systematic review articles, one that I conducted along with Elaine Larson in 2002, that looked at the evidence for a causal link between hygiene and infections, a study by Curtis and Cairncross in 2003, and then a study by Meadows and Le Saux.

We then searched the PubMed database for other articles from 1980 to 2005, and we used various key word combinations including things like

hygiene, infection, soap, and washing.

[Slide.]

So, for our inclusion criteria, the studies needed to have an outcome of either a culture confirmed infection, symptoms of infection, or absenteeism associated with infectious illnesses, or it could be a combination of these, so specific infections, as well as absenteeism.

So, the study designs that we were looking at had to be community based, so they couldn't be conducted in the clinical setting, so, for example, they couldn't be conducted in a long-term care facility or hospital setting, and they had be an intervention study, because of a lot of the confounding and bias issues that Steven spoke about, that at least would control for some of that.

Then, we also included cross-over intervention studies, and we included both of those with or without formal randomization, and when I am speaking about formal randomization, I am talking about studies that use random number generators to

actually randomize the intervention arm.

So, the intervention arm had to provide for the study to be included, either a plain soap, and I say in parentheses here "not identified," because in some of these studies, they didn't identify the ingredient in the soap, so we will just say we gave soap, they don't say that it was plain or non-medicated, but we included all those studies together.

We then looked at those that identified antiseptic soap in comparison to either a placebo or a no-soap control arm, and then alcohol-based hand sanitizers, as well as the non-alcohol hand sanitizers.

[Slide.]

So, these are the numbers of studies that met our criteria. For the soap, it was either plain or identified, there was 8. For antiseptic soap, we found 5. For alcohol-based hand sanitizers, there were 9 that met this criteria, and then for non-alcohol-based hand sanitizers, we found 2 studies.

[Slide.]

So, these are the 8 studies that were conducted in plain or unidentified soap versus a

control group, and of those, only 3 were formally randomized. The soap form was bars for all the studies, and the number of studies that reported that they actually were using plain or non-medicated soap were 4, and then 4 didn't mention what type of soap they were using.

There was an educational component asking to wash the hands at critical points in 7 of the studies. A few used hygiene promotion seminars, 1 used washing of dishes, and another, the only 1 study asked the study participants in both arms to follow regular routine.

[Slide.]
The outcomes included diarrhea incidence, also diarrhea prevalence, healthcare visits, and even one study looked at culture-confirmed Shigella species infection. Two studies looked at impetigo. One study looked at skin and eye disease, and then one study looked at runny nose, cough, and

pneumonia.

[Slide.]

The exposure measurements were measurements of soap or handwashing, and only 6 studies actually measured this, and it was extremely variable in the way that they measured it, and as far as controlling for confounding, at least mentioning controlling for confounding, or reporting balance on covariates at the baseline, there were 7 studies, and this again was extremely variable, but as it increased from 1980 to present, more and more studies started to include confounding issues.

[Slide.]

So, this is the reduction in diarrhea incidence for the studies that looked at diarrhea incidences and outcome, and as you can see here, the reduction, and the way that we calculate the reduction is basically you just, so say if the incidence rate, for example, is 0.60, then, the reduction in risk, because you are looking at the intervention versus the control, would be 40

percent, so that is how you calculate the reduction in diarrhea incidence.

You can see here that there was a pretty strong reduction in diarrhea incidence, so this is comparing just the plain soap with a control group that received nothing.

[Slide.]

Other significant findings for other outcomes, the Luby study in 2005, a recent study, found significant reductions in all these other outcomes, cough, runny nose, pneumonia, and impetigo, but for the one study where there was no prompting of a change in hygiene, so they just provided the soap, and that was it, they were looking at an outcome of impetigo, and there was no significant difference when there was no education component included.

[Slide.]

So, the reduction in incidence of diarrhea ranged from about 30 percent to 89 percent. The median reduction is 53, and there was a similar reduction in range for other outcomes in the one

study by Luby.

[Slide.]

So, what about the study design issues? Well, most studies prior to 2004 lacked formal randomization. It wasn't possible to mask participants or interviewers, of course, because one group has the soap product, the other is a control group.

Only two studies used techniques to control for clustering, and Steven mentioned that. That is a huge issue because it can bias the estimates, it can actually provide an overestimate of the reduction that is truly achieved.

Limited measurement on hygiene and soap use information.

There was varying definitions of symptoms and reporting across studies.

All of these studies were conducted outside the U.S. in very high-risk populations, so the reduction in estimates that we see are probably much stronger than what we might see here in the U.S.

Very difficult to tease apart the effect of the soap use from that of the hygiene education, and the only one study that had baseline didn't ask

anyone to change their habits, and had them do the same thing, did not find a significant difference between the groups.

[Slide.]

So, in general, there were consistent reductions observed regardless of these varying methods, potential biases, and study population variability.

Plain soap in conjunction with the proper hygiene education does appear to be effective in reducing diarrheal illness in high-risk populations, and it is not as clear with other infection, because there is not as much data to have examined that.

[Slide.]

Now, what about antiseptic soap versus plain soap? We found five studies, and they started in 2002 and up to the most recent in 2005. Most of these were the studies by Luby, and one study was

by Larson, and the studies by Luby took place in Pakistan, and the Larson study was here in the U.S.

[Slide.]

So, for the comparison groups, two studies looked at the relationship between the antiseptic soap versus plain soap, so they had a placebo, so there was blinding there.

Then, there is what Steven had spoken about, antiseptic soap versus the plain soap and also a control group arm, so there was three arms to the study.

Three of these studies used formal randomization, and the soap forms were bars for four of the studies, and one was the liquid soap containing triclosan.

There was an educational component in three of the studies, and following regular routine in two of the studies including the Larson study.

[Slide.]

There was various outcomes looked at: diarrhea incidence/risk, impetigo, pneumonia, and symptoms of infection.

[Slide.]

Measured soap use or handwashing was done in four of the studies, and four masked

participants and interviewers only again amongst the placebo groups.

Controlling for confounding was reported in five of the studies and balance on covariates, so these studies were definitely much more rigorous than the studies that we found on the soap alone in general as far as controlling for numerous confounding factors, such as hygiene habits.

[Slide.]

So, now, this is the reduction in diarrhea incidence. We just pulled this because there was two studies that both looked at this as an outcome.

So, for the Larson study, they reported a 10 percent reduction, but it was not statistically significant, and in the Luby study, it was actually higher when you compare the incidence rates in the antibacterial group compared to the control group.

None of these were statistically significant. The Luby study also was not designed

or powered to make the comparisons between the plain and the antimicrobial group.

[Slide.]

So, this is a reduction in incidence of the other symptoms, and again there is no statistically significant differences in these other symptoms of infections, such as cough, runny nose, and impetigo or skin infections.

[Slide.]

Then, when we look again at the relationship between the antiseptic soap versus the control group, so there is nothing in this control group, which is an extremely high-risk population. As you would expect, you see reductions similar to the soap reductions in impetigo and diarrhea in these children in Pakistan.

[Slide.]

So, there is no statistically significant differences for all infectious symptoms in the antiseptic groups versus the plain soaps for the three studies that compared these groups.

The antiseptic soap versus control group,

again, we saw the reduction in incidence that was ranging from 29 percent to 50 percent, and was very similar to the reductions associated with the use of plain soap.

[Slide.]

So, as far as the study design limitations, Steven went over some of them already, again, the possibility of viral or parasitic etiology and the fact that the children were in very high-risk groups as far as infection.

The study design strengths are that all the studies used techniques to control for clustering, so at least these studies were controlling for the clustering issue using a statistical method to control for that.

All the studies measured baseline hygiene information. One looked at these practices over the duration of the study, and two did product monitoring, so, for example, the Larson study actually weighed the soap use and asked the people about how much they were using.

Three studies masked participants and

interviewers by use of a placebo, and there was extensive follow-up for symptoms.

[Slide.]

Right now, as far as the conclusion from the research that we have available, there is a lack of evidence that antiseptic soaps provide a benefit beyond plain soap in the community setting in both U.S. and Pakistan. This was two areas where it has been tested. That includes for diarrhea, impetigo, as well as other infectious symptoms.

When compared to a control group, if you compare the antibacterial soaps to the control group, where there is no soap or hygiene education, antiseptic soap with hygiene education is an effective intervention for reducing impetigo and diarrheal illness in high-risk groups.

[Slide.]

So, what about the alcohol-based hand sanitizers? Now, there were nine studies that met the criteria for our research.

[Slide.]

There were various comparison groups used, so the majority of the studies looked at alcohol plus an education intervention versus a control

group that received nothing.

Two studies of alcohol plus education versus a control group that at least had education, so they were somewhat comparable at baseline, and then one study looked at alcohol versus control group that had nothing, and no education component.

Four of these were formally randomized, two were cross-over studies, and there was various alcohol forms used, so the earliest study coined the term "alcohol hand rinse." It is not clear exactly what they were using, but it had 60 percent isopropyl alcohol.

There was disinfectant in two studies, foam, as well as predominantly instant hand sanitizer.

[Slide.]

Now, the outcomes were similar. They looked at GI illness, upper respiratory illness. Some were more specific, they looked for viral

respiratory illness, and then symptoms of infection, as well as absence related infections.

So, the individual would be asked, you know, why was the child absent, and they would have to say the child had either a GI symptom or respiratory illness, and that was the reason for absence.

[Slide.]

So, three measured the alcohol use by either supplies, and then one actually asked about frequency of use, one asked about total hand hygiene practices, but, in general, these studies are not inquiring about handwashing in addition to the use of the alcohol-based product, and none masked participants or interviewers except for one study where they collected illness data from the parents who were masked to which intervention the children were in, so they didn't know whether their school was in the intervention or control group. So, at least the reporting of the symptoms may be a little bit less biased in this study.

Then, four studies controlled for confounding or reported balance on covariates at

baseline.

[Slide.]

So, these are the estimates for the reduction in diarrheal illnesses, and so there was three studies that had this as a specific outcome, and you can see that the range of reduction is pretty strong, and they were all statistically significant reductions.

[Slide.]

This is respiratory infections, and this is a bit different. You can see that there was only one study that was statistically significant, and the other three studies did not show a significant reduction in respiratory illnesses.

[Slide.]

We then look at symptoms of infection, so this is various infections. It could be GI and upper respiratory illnesses lumped into one sort of a mixture for absence-related infections, for example, and you can see the range here is larger.

[Slide.]

The reduction in diarrheal illness ranged

from 48 percent to 71 percent, and these are similar to reductions associated with the use of plain soap.

Most reductions in respiratory illness were not statistically significant, ranged from 3 to 20 percent.

Infectious symptoms/absences ranged from 9 percent to 43 percent, and this isn't surprising that we see this variability because of the way that they were measured were very different between studies.

[Slide.]

What about the study design limitations? Again, there is the issue of unknown etiology for the symptom definitions. There is only one study that actually did culturing of infections and for viral infections. There is a lot of variability in the definition of symptoms and reporting methods in these studies.

They are not, on average, balanced on education intervention. There is a lack of consistent measurement of alcohol use and other

hand hygiene practices, and we don't know much about soap use.

Again, it is difficult to employ masking, so, for example, the Sandora article, the most recent article in 2005, mentioned that, you know, they had considered using a placebo, but for one thing, it is difficult to formulate a placebo that would smell like alcohol and act like alcohol, and secondly, they didn't feel that it was ethical to do such a thing because they were asking people to use this product at critical points, and using something that had no efficacy would be unethical.

Only one study controlled for clustering, so that is the most recent study, the Sandora study actually used statistical measures to deal with the clustering issue.

[Slide.]

So, alcohol-based hand sanitizers, in conjunction with a hygiene education, seminar or information, can effectively reduce diarrhea and general infectious symptoms in the community setting.

As far as the question of alcohol alone, it is difficult to say because of the way that the studies have been imbalanced in terms of the

education.

There is less evidence of effectiveness for reducing upper respiratory infections.

[Slide.]

So, for the future research needs, there needs to be an assessment of the effect of antiseptic soaps and alcohol-based hand sanitizers in culture confirmed viral and bacterial infection studies. So, this is important.

If the argument is that these antiseptic products are not effective against the way that we are collecting the data on the infection outcomes, then, we need to know exactly what organisms they are effective against and actually look at the types of organisms.

The other issue is to assess the benefit of alcohol-based hand sanitizers in groups with similar baseline levels of hygiene education.

One of the things I am also working on,

too, is looking at the effect of education alone, so the effect of education independent of all of these other products as an intervention.

What I am finding so far in our preliminary results is that we see about an average of about 25 percent reduction, so in these studies we are seeing about a median of a 50 percent, so what we want to do is try to make comparisons between these different types of reductions.

So, there may be some added benefit, but, you know, are we overestimating the benefit, and we want to know that.

There needs to be better control of confounding in these intervention studies. There needs to be a much larger discussion on the baseline comparability of the two intervention arms at the outset of the study, for example, and the use of the products at the beginning.

We need analytical techniques that accommodate the clustered data. I mean this is an issue for power in sample size, for example. You know, if they are doing these cluster randomized

studies, that does reduce the ability to detect differences between the intervention and control groups, and we also need further household level studies.

A lot of the studies have been conducted in daycare centers and schools, for example. We need further studies within the household level, so we know what is happening at the community level.

That's it. Thank you.

DR. WOOD: The next speaker is Stuart Levy.

The Potential for Antibiotic/Biocide Cross-resistance

DR. LEVY: Thank you very much. Thank you to the organizers.

I want to say at the outset that the firm that was mentioned early on is Paracheck [ph] Pharmaceuticals, and we are not in the business of making antibacterial consumer products, but I am president of the Alliance for Prudent Use of Antibiotics, whose mission is to see that antibiotics retain their efficacy in the treatment

of human, animal, and agricultural disease.

[Slide.]

Another point. I have an issue, and those of you that know me know I have an issue. My issue is not with the non-residue antibacterials, so I separate out alcohol, bleaches, and peroxides. They do their job, they are gone, they don't leave residues.

So, I have another issue, and that is with what I heard earlier, that one of the goals for a consumer product that it persist, and persistence is, to me, contrary to what I want, because I see persistence as leading to resistance.

So, at the outset, that is really, if I didn't say anything more today, this is the message I want to give.

[Slide.]

Resistance can come to biocides and antibiotics by a number of means. First, it can be a target mutation. I will show you an example. Another is through an efflux system, a pump that pumps out antibiotics, biocides, organic solvents,

you name it, and they exist in all bacteria. They are a real problem in pseudomonas and some of these gram-negatives, but they are also a problem in gram-positives.

Finally, there is this co-resistance, the difference being cross-resistance is the same mechanism, the pump, the target that will give you resistance to the biocide and to the antibiotic. Co-resistance means that they move together, they are linked on a plasmid or on a transposon.

[Slide.]

The example of a target mutation is triclosan, and historically, I mean I didn't know what triclosan was when I was called by a consumer who said, you know, there is triclosan in all these products, in toys, and so forth, is that a problem? You have been preaching about prudent use of antibiotics. This is an antibacterial.

So, after a few of these calls, I turned to my associate, Laura McMurray, and I said, Laura, maybe we should look into this. So, what she did was to find whether or not resistance was easily

gotten to triclosan, which had a long literature, we are talking about decades, but not anything really dealing with mechanism of action or mechanism of resistance.

[Slide.]

So, she did a classic genetic experiment. She put E. coli on a plate with triclosan and isolated mutants easily, overnight, spontaneous, and those mutants all were in a single gene, the fabI, the fatty acid biosynthesis gene I. They had different mutations, and the mutations correlated with a different fold in the resistance, or shall we say, insensitivity to the drug, low, medium, and high.

Because the enzyme had been crystallized, one could look and see that, in fact, these mutations could well be within, and were within, the substrate binding site.

[Slide.]

The other interesting feature was that the fabI gene was a homolog or ortholog of an important gene, a target for isoniazid in tuberculosis, and

while there has been a discussion as to whether inhA is or is not the target, I think, at least I hope, it is now agreed that there are two targets, a catalase and inhA, and, in fact, this is the classic or shall we say the real target if you are going to look at inhibition by an antibacterial antibiotic.

There is this diazaborine, which Sandoz was developing it, its target was fabI. We used it to demonstrate that our mutants were also resistant to diazaborine. I would like to also say that at least two companies had decided that the fabI gene was a good new target for an antibacterial or antibiotic, I should say, and it turns out that the mutants that we had isolated to triclosan were resistant to these newer or shall we say not yet launched, and probably not going to be launched, new antibiotics.

[Slide.]

What about the cross-resistance? Is inhA or triclosan or, shall we say, fabI gene going to give you resistance to isoniazid?

Well, here is an experiment we published, which shows that if a mutant MT1, for instance, is selected by triclosan, we see where the mutation

is, and then we look and we see that it's 6-fold more resistant to triclosan and 8-fold more resistant to isoniazid.

This is in Mycobacterium smegmatis.

If you then go to a mutant that Bill Jacobs isolated, the MC2651 that was selected in isoniazid, it has a mutation, and we see that it has 6-fold resistance to triclosan. Never saw triclosan before, and a 22-fold resistance to isoniazid. So, this is what we call cross-resistance.

[Slide.]

There is another mechanism across resistance which doesn't deal with the target, and doesn't really have anything special about it except that they are protein pumps, they come in single protein varieties or three protein, a tripeptide, that is, there is there an inner membrane, there is a periplasmic, and an outer

membrane, and these pumps are very good at pumping out antibiotics where they were first discovered, and now, more recently, with biocides and other agents.

[Slide.]

This is a pump, an E. coli, Klebsiella, Enterobacter, the Enterobacteriaceae. It was originally described many years ago. It was an acrogene, resistance gene, only later now demonstrated to be any flux pump, acrAB.

We have been studying a regulatory gene called mar, which, in fact, upregulates the acrAB gene. Now, this efflux gene can be upregulated by mutation in its promotor, in its represser, or by upregulating these other outside regulators like the marA protein or the soxS protein.

So, there is a lot of ways to get this efflux pump up in the enterobacteriaceae, but it's not just acrAB, there is an EF, there are many of these multidrug efflux pumps.

Why is it important? Because look at what they do. They pump out antibiotics, organic

solvents, pine oils, bile salts, triclosan, chloroxylenol. They don't care what they see, they are going to protect their host, and they have to think about it then, so are we worried? What are we worried about?

We are worried because that means that an antibiotic can select this kind of mutant and make it resistant to biocides that we may want to use to protect multiple patients, or we could be using a biocide which selects a mutant, which now is resistant to antibiotics, and we are not talking about just one, we are talking about tetracyclines, penicillins, fluoroquinolones, chloramphenicol.

[Slide.]

An example of these kinds of biocide resistance, antibiotic resistance, efflux pumps is here. There are many others, but I included this because of the real impact on Pseudomonas aeruginosa, which is the basis for its multidrug resistance, the principal basis for its resistance to all drugs, making it one of the most important and difficult pathogens to treat in our hospital

today, we have Pseudomonas, we have Acinobacter, and we have Stenotrophomonas.

All of these have these pumps that pump out antibiotics, and it turns out they pump out biocides. They do it the same way I showed you with E. coli. Either the pump is already upregulated, or a regulator of a pump gets mutated, or an outside regulator pumps it up like the mar.

So, these examples are out there, but they are dealing with important pathogens, also pathogens that are opportunistic and pathogens which really would call commensals. I mean a Pseudomonas aeruginosa for anyone else is usually not a problem, so if it's in the household or if it's in the wake of a use of this, you can really imagine and see how these kinds of resistant mutants can be selected.

[Slide.]

What about co-resistance? And there are lots of examples of these. There are plasmids which are outside of the chromosome, which are unique and they replicate by themselves, and they

carry genes which are supplemental to the host.

In the early days, these plasmids contained genes, some of which we don't even know about, some have to do with toxin production, we are not quite sure why they held on, but we now know about them because they have resistance to antibiotics, and they have been picked up actually over the past four or five decades, probably five or six decades of antibiotic use.

What is of interest is that one of the ways that these plasmids accumulate resistance gene is by an intricate and actually elegant genetic mechanism, which we call an integron discovered by Ruth Hall, and this is almost, and for my mind I look at it like a venus fly trap, something goes around, there is a gene for resistance, and it kind of sucks it into the chromosome or into the plasmid, and now you have two genes for resistance, then three genes, and interestingly enough, one of the fundamental early genes for resistance was their resistance to quaternary ammonium compounds, the so-called QAC efflux pumps that are present in

staphylococcal plasmids.

[Slide.]

Here is an example from Dr. Sidhu where he shows the blaZ gene there, beta-lactamase genes associated on the same transposon, on the same plasmid as resistance to quaternary ammonium compounds.

So, what do you use? Is a Qac going to select for the plasmid or is it going to be a beta-lactamase, or is going to be another antibiotic, because these integrons can have five, six, seven different antibiotics, and they are all going to be selected at the same time.

We are talking about population dynamics. We are talking about selection. We are talking about inability to use the antibiotic or the biocide. I am not saying that there is not a place for biocides, but what I am going to say is that I don't see that they are needed in the consumer product.

[Slide.]

We also have learned, and are still

learning, lessons from antibiotics. We have learned how we have misused them. We have also learned how bacteria come back to tell us how we misused them.

I remind my students that bacteria are not going to be destroyed. They have been here, they have seen dinosaurs come and go, and they will be happy to see us come and go, they are not going to leave.

So, any attempt to try to sterilize our home is fraught with failure, and so what we are seeing is evolution in action, because we start out with a bug which has decreased susceptibility to a drug, and it still is susceptible, but it is not quite as susceptible, but eventually becomes resistant to that drug.

In the clinical world, we have many instances, but some of the most relevant recently are penicillin-resistant Strep pneumo, which get their resistances by picking up pieces of the penicillin binding proteins from other bacteria in the oropharynx, the Strep midas, the Strep

viridans, which are intrinsically resistant.

So, they accumulate them. They start out with twice the MIC, but we can still treat them until they get to high level, and what is the high level? A totally mosaic penicillin binding protein, which is not a target for penicillin.

Fluoroquinolone resistance. When fluoroquinolones came out, you can't get a mutant. We put it in the laboratory. Interesting phenomenon. You can't get it in the laboratory, but we certainly have it out in nature. We have it in our clinics, and it is multiple mutations in the target gene and in efflux pumps. Gradually, over time, like TB, but we never expected it in something like an E. coli, and we see that in all the enterobacteriaceae.

The last one, of course, is the vancomycin- resistant Staph aureus, which began by becoming chromosomally resistant, lower level, intermediate, still cause some failures in treatment until it acquired the vancomycin resistance transposon on a plasmid from the

enterococcus.

[Slide.]

So, this early sign of decreased susceptibility, to me, is a worrisome sign. That tells me that I am starting these bacteria on the road to full resistance. This is a study that we did with Allison, Elaine Larson, and others, looking at the effect with or without antibacterial hand soaps on the microbiology of the skin flora.

No statistical difference seen, so start right out. We saw trends, but no statistical significance, but what we did see was in the home, on the hands, a disconcerting finding that there were Staph aureus, Staph capitis, and other staphs that had eschewed their susceptibility profiles up to the 2 and 4, and there have been reports from Molly Schmidt and others that show that staph is there, it's moving, more populations of staph are becoming less susceptible, do we know what it means by resistance? It may be that the biocide wouldn't work against these. These studies have not been done.

[Slide.]

Look at Klebsiella, a problem, a big problem in our hospitals, and we would love to be

able to say that we can keep control by using something like triclosan or other antiseptic or antibacterial of this type surface in the hospitals, but look, we had a Klebsiella that was growing in 32 micrograms/ml of triclosan.

That, to me is not tolerance, that is resistance, and we are seeing this eschewance, as long as we see this happening, that's a sign that full-fledged resistance is on the way.

[Slide.]

This is a paper presented by Fred Goldstein last year, unexplained, but I think it's important. He looked at glycopeptides. This is vancomycin intermediate Staph aureus, so-called GISA strains. That is that intermediate strain before it developed and actually acquired the enterococcal vancomycin resistance transposon.

Looked at 45 of these strains, 24 just methicillin-resistant staph, 28 MSSA. More than 84

percent of the French GISA stains had a triclosan MIC of 0.5 to 2 micrograms, about 100-fold higher than most MRSA or MSSA. For GISA and other MRSA, but not MSA, a 2- to 4-fold MIC increase has been observed for benzalkonium chloride, 2 to 8 for chlorhexidine, and 6 to 4 for hexachlorophene.

I don't know what it means. I am just saying that these are the kinds of bacterial strains that they are facing in French hospitals. How did that arrive at? Could be vancomycin, could be the antibacterials, but we have either co- or cross-resistance in these organisms, and it is trying to tell us a lesson, that we should be cautious and we should be concerned, because if, in fact, we are trying to control a GISA in a hospital, we may well want to use triclosan or a QAC.

[Slide.]

A study done in Japan a number of years ago was somewhat telling to me, and I have mentioned it, because they took an MRSA, and it began with a susceptibility MIC benzalkonium

chloride of 5, and they just raised and picked mutants at 10, and looked at the dramatic change in the susceptibility to the penicillins.

The oxacillin goes from 16 to 512, clox from 0.5 to 256. Unfortunately, the investigators didn't look at the mechanism, but it does indicate that you can get, in the selection process, and it is in the laboratory, cross- or co-resistance to very valuable antibiotics along with a decreased susceptibility to a biocide.

I will say if you can do that in laboratory, it can be done in nature. We had trouble getting fluoroquinolone resistance in the laboratory, we have no problem seeing it out there. It is a question of volume and time.

[Slide.]

Here is another benzalkonium chloride story, and this is with E. coli, and the circles in red are those in which the organism had been adapted to growing in 150 micrograms/ml of benzalkonium chloride, and you saw cross- or co-resistance to penicillin, the fluoroquinolone,

chloramphenicol, tetracycline. They do exist.

[Slide.]

So, in our study, we asked the question: If you are using an antibacterial soap or a plain soap, do you have more resistance, less resistance, the same amount? The answer is the same. You see the dark bar is higher for antibacterial, but it is not statistical.

So, someone will say, "Well, there you go. After a year of use, there is not a problem."

Well, the problem is that, one, the homes had a lot of antibiotic resistance, and where did that come from, so we are starting at a high level, and, two, we learned from antibiotics it doesn't happen in a year, it can take much longer, but what we are seeing in the laboratory, what we are seeing out there in the clinic, the co- and cross-resistance should tell us that we need to be careful how we use these drugs.

[Slide.]

So, it comes back to the same story. If I use penicillin and I use Staph aureus as an

example, penicillin was used.

[Slide.]

There were penicillinases out there, they were selected. Methicillin was invented, what happened? Bugs came up with methicillin resistance, which was, in fact, a transposable element.

Then, MRSA, we began to treat with vancomycin. We got the intermediate, the GISA strains, like I showed you, the GISA strains, and with time, VRSA. Now, what is going to stop that phenomenon occurring if one continues the volume of use of biocides in the consumer market? Volumes, volumes.

[Slide.]

So, anyone asks me what is the problem with antibiotic resistance today? Dr. Levy, does it come from biocides? I say no, it comes from misuse of antibiotics, but I don't like this mounting increase of co-selectors of antibiotic resistance and the resistance to agents that we have a place for in the healthcare market by the

volumes of use in homes casually used by consumers, and we learned today it makes a big difference how you use them, and I can tell you, in our look, you know, if it's a 3- or 4-second wash, that's fine, and they are left there as a residue, because as I said before, I am concerned about the persisters.

[Slide.]

So, this is the today. I am happy if we can keep it this way. I don't want a tomorrow. By that, I mean where biocides are equal or prominent contributors to the drug resistance problem, and from my perspective, with the studies we have done and what I have seen from other laboratories, I think this is a concern we should consider.

Thank you.

DR. WOOD: Thanks to all the speakers. We are right on time, so let's take a brief break and be back ready to start at 9:45.

[Break.]

DR. WOOD: Let's get started. Go ahead.

Secondary Routes of Exposure to Biocides

DR. HALDEN: Good morning. My name is

Rolf Halden.

[Slide.]

I am going to talk about secondary routes of exposure to biocides.

[Slide.]

Before I get started, I would like to give you some background information.

[Slide.]

In terms of environmental health, we study contaminants that are potentially toxic, that are produced in large quantities, that are environmentally persistent, and we know that humans actually get exposed to these chemicals.

Sometimes these chemicals are also difficult to detect. Any of these characteristics here makes for an environmental contaminant that deserves our attention.

[Slide.]

If we look at the chemicals that are under review today here, we can single out maybe two out of the six that partly fit the picture here of potentially being problematic. These are triclosan

and triclocarban. Anything I say today here will relate only to these chemicals. I don't want you to extrapolate from my talk to the other chemicals that are under consideration here.

Triclosan and triclocarban were introduced to the market in 1964 and 1957. They came from the hay days of making aromatic compounds, putting chlorines on, and using them as pesticides.

We had DDT. We made PCBs in those times. A lot of these chemicals have been banned now. However, we still use triclosan and triclocarban. Why are we potentially concerned about these chemicals?

Well, to start off, they have aromatic rings, which sometimes are difficult to degrade, particularly if the hydrogens are replaced with chlorine atoms, which we have three incidences here in both triclosan and triclocarban.

These chemicals, they don't like water. They don't like to swim. Whenever they get an opportunity to leave the water, they will do so, and they really like fat, and unfortunately, we are

fat, so if they have a choice, they will leave the water and come to us, and then they stay with us.

So, if we have a glass of water containing 1 molecule of triclocarban, for example, we can expect if there is a fat phase right next to it in this free exchange, that we find 100,000 molecules of triclocarban in that fat phase.

[Slide.]

I got interested in triclocarban about three years ago. I was doing a literature search and found that both chemicals are used and produced at the same rate, and when I looked at the literature, this is what I found.

Essentially, every three days I have to read a paper on triclosan, but if I want to be lazy, I can just study triclocarban and sit back and, you know, watch the sun go down, because there is no publications on triclocarban despite the fact that it has been produced longer than triclosan.

[Slide.]

Let's take a look at triclosan first. We know much more about it, so I think it is fair to

cover this first. The life kind of cycle of triclosan, when we make triclosan, we produce dioxin, 2, 3, 7, 8-hydroxldibenzoparadoxins. It's a human carcinogen. It is produced in very small quantities, but triclosan is a precursor of dioxin.

When triclosan is in water, present in water, and illuminated with light, it can form 2-chlorodibenzoparadioxin. Triclosan is persistent because it is a chlorinated aromatic, it's a binuclear aromatic compound. We have heard about cross-resistance to antibiotics, so there is firm data assuring us that this can happen. How important it is, I leave this to the experts.

Chlorinated aromatics do bioaccumulate. There is many examples, and triclosan is not an exception here, so there is no surprise this chemical has been detected in fish, for example.

There is speculation that triclosan might function as an endocrine disruptor. There is really no firm data on this. There is one paper that explored this in a little more detail, but I don't think we have answered this sufficiently.

Sometimes people ask when they chlorinated aromatics, are these carcinogenic, mutagenic, teratogenic compounds, and for triclosan, we have

to say that the chemical itself probably is not, but possibly, you know, some of the impurities, for example, dioxin.

[Slide.]

Let's take a look at triclocarban. Much less is known about this chemical. It is conceivable that when you make triclocarban, you use as a precursor chemicals that look like the chloroanilines. There are known animal mutagens and known animal carcinogens.

When triclocarban degrades, we know that the major metabolites are also monochloral and dichloroanilines. Again, these are known animal mutagens and carcinogens, and probable human carcinogens. Triclocarban is persistent. This was established fairly recently.

Triclocarban, can it cause cross-resistance to antibiotics? I haven't seen any studies; if you have any, please let me know.

Since it is structurally related to triclosan, maybe it has similar effects.

Bioaccumulation, again, very little data, the data is just being produced right now because we start to look at the environmental fate of the triclocarban. Endocrine disruption, again, we have no information on this.

Is there a link between carcinogens or between triclocarban and cancer and mutations? There is a conceivable link because of the structural disintegration of triclocarban to the known mutagens and carcinogens.

[Slide.]
Again, since there is no information on the environmental fate of these chemicals, we did some quantitative structure, activity relationship analyses suggesting that the half-life of both triclosan and triclocarban is very short in air, somewhat longer with two months in water, and fairly long in soil and particularly sediment.

Sediment is the muck underneath the water column and surface water, and your water resources,

so we see that the half-life can be as long as one and a half years estimated from these models.

[Slide.]

I would like to move on now to exposure assessment.

[Slide.]

Obviously, whenever a chemical is introduced, we test it and we make sure that it is safe, and we use our best estimate as to what the route of exposure is and then study that in depth.

So, for example, for personal care products that are labeled topical antiseptics, we study whether they absorb through the skin. We don't study, you know, what happens if you eat large quantities of them, for example, because nobody is expected to eat the soap bar.

But we can acknowledge that there are other routes of exposure other than the one that we intend. So, in my talk further on, I would like to make the point that there is a potential route for the migration of triclocarban in the secondary route of exposure through the food chain.

This starts by when we are done with using the soap, it is disposed of into wastewater. The wastewater is treated in wastewater treatment

plants. We have more than 18,000 in the country, and they make a lot of sludge.

It turns out that triclocarban accumulates in sludge because it doesn't like to swim, as I mentioned. If it doesn't find fat, it goes into the sludge. The sludge is being applied on soil partially, and on the soil we have either animals grazing or we have crops eventually grown, so there is a potential link to the food chain, and then obviously, this would lead to ingestion.

[Slide.]

Are there any firm data on this hypothesis or speculation at this point?

[Slide.]

Let's take a look, biocides in aquatic environments. Again, due to the drought of papers, we published a paper last year, and it turns out to be the first paper examining the environmental fate of triclocarban. I think this is unprecedented for

a chemical that has been used for 50 years as a high-production volume chemical, nobody has ever bothered to look what happens to it in the environment.

[Slide.]

So, we put out this paper, and essentially, we just showed, hey, if you are interested, use this method and you can find this chemical. We used it and just took some water samples along six urban streams in the Baltimore area, and we found the chemical in each stream we examined, not in every sample, but certainly in every stream we looked at, and the concentrations ranged from the high nanogram per liter range to below the detection limit.

[Slide.]

What you see here to the very right is raw sewage as a comparison entering the wastewater treatment plant locally, and these are concentrations of triclocarban in Gwynns Run, a highly contaminated stream that is impacted by leaking sewer lines, so there is raw sewage flowing

into the stream. Obviously, this is a worst case scenario, and you shouldn't extrapolate from these data to ambient levels you would see typically in the environment.

[Slide.]

A fascinating observation that we made when we looked at both triclosan and triclocarban is that they are co-occurring, and I think if you look at the structure I make that point, only you have 2 benzene rings, you have got 3 chlorines, they look very similar, so maybe it is not as surprising that they behave similarly, too, and since they are produced almost at identical quantities, you can come up with this correlation, and essentially, if you can measure one chemical, which is triclosan, then, you can calculate what the approximate concentration of triclocarban is.

[Slide.]

We did this and published another paper where we suggest that about 60 percent of U.S. water resources have detectable quantities of triclocarban.

[Slide.]

We arrived at this prediction by using a dataset from the United States Geological Survey

that had looked for 95 different chemicals in streams, in 139 streams nationwide. Unfortunately, they did not consider triclocarban, but we used the detections of triclosan and applied our model to then predict what we think are likely concentrations to have been present at that time in those streams.

[Slide.]

Here is a map showing that essentially, we have complete coverage of the United States, and there is a number of locations where concentrations exceed 100 and 1,000 nanograms/liter, so we are then in parts per billion range.

[Slide.]

Obviously, this is just a prediction. We are working right now to either confirm or not the hypothesis that the chemical occurs, and we have a large sampling network across the United States, and have some initial data generated by one of my

graduate students.

[Slide.]

The initial data were coming from nine states from across the United States. Again, we predicted that triclocarban is present in 60 percent of the U.S. water resources. Experimentally, we determined so far that 56 percent of the stream samples taken upstream of wastewater treatment plants have detectable levels of triclocarban.

If you look downstream where the water has been discharged, you find it in every sample you look at so far. The concentrations are lower than the ones we predicted. This is not a surprise. The USGS, when they went out first and looked for 95 chemicals, they had in mind that, you know, hopefully, they would find something, otherwise it would be hard to justify expending all this money. So, they went to the locations where they expected streams to be susceptible to contamination.

Therefore, what we see in the USGS data are kind of worst-case scenarios.

[Slide.]

So, again, we find the chemical in most of the samples, and concentrations are low. If you

take a look at the units here, we are talking nanograms per liter, parts per trillion. These are really levels that a few years back, we didn't think about and we couldn't measure.

[Slide.]

As opposed to the aquatic environment, let's take a look at the terrestrial environment, and take a look at concentrations there. I think you will be surprised to see what we have there.

[Slide.]

This is an image here of a typical U.S. wastewater treatment plant.

This particular plant processes 180 million gallons of sewage a day. It does so day-in day-out, and serves 1.3 million people. It is located on the East Coast. If you don't know how a wastewater treatment works, here is a crash course in 15 seconds.

[Slide.]

The water goes through a screen. It hits a primary clarifier. Some of the solids are lost, and the water flows into kind of a whirlpool of microorganism where you blow in air. Some of the contaminants are degraded, and then you settle out the sludge, and the water is sometimes chlorinated,

as in this plant, filtered, and then discharged back into the stream.

This is a good thing. We need to recycle water, we don't get a new molecule, we have to use what we have got. It's all re-used, so there is no issue with that.

We also produce quite a bit of sludge in the process. The sludge from this plant here is being digested for an approximate period of three weeks anaerobically, so we have an aerobic treatment process and an anaerobic treatment process.

Then, we have what we call biosolids if we dewater it. It can be Class B, so with quite a few pathogens, or Class A, a little cleaner.

[Slide.]

We took an unusual approach of doing a mass balance. If you look at the literature right now for triclosan, you will find a lot of papers showing you this type of data. There is raw sewage coming into the plant. You have concentrations less than 10 parts per billion.

If you look at the effluent, it is less than 1 part per billion. The plant does a wonderful job, it is great, and you often read that

this is due to biodegradation, but it is due to the absorption of the chemical to particles because it doesn't like to swim.

[Slide.]

If you look at the concentrations of sludge, and this is a semi-log plot, so what you see is that the concentrations are 3 to 4 orders of magnitude higher in the biosolids.

So, here we have digested sludge, which is municipal sludge, and now we are talking concentrations of milligrams per kilogram. This is actually 6 orders of magnitude higher than the nanograms per liter that I showed you previously.

[Slide.]

Let's take a look at what really happens to these chemicals. If we track the mass coming in and track the mass going out in liquid and going out in the solids, assuming that nothing volatilizes, we can do a mass balance on this.

[Slide.]

The red piece of the pie is the fraction that we believe is not degraded. I have to tell you, unfortunately, that these data are very conservative. These are estimates we published last year at the ACS meeting. In the meantime, we

have submitted manuscripts showing that the

fraction of TCS and TCC, which is triclosan and

triclocarban, are really greater. So, less than a half of the chemical is being durated in the plant.

So, the life is not over when this

chemical has entered the wastewater and went

through the wastewater treatment plant.

Let's see what is next.
[Slide.]

In the United States, we can't dump sewage

into the ocean anymore. The decision was made that it's not a good practice, so we have to do something else with it. Some of it is incinerated, some is landfilled. A lot of it goes back to agriculture.

This not new news, it has been done for thousands of years. It is good practice, it has lots of nutrients in there. There is also other things in there, including triclosan and triclocarban.

What is happening in the wastewater treatment process is astonishingly, that you have a huge volume. Again, we are talking in millions of gallons of liter, very dilute concentration, and a lot of interest.

It all gets compartmentalized and accumulates to 6 orders of higher concentrations in this biosolids or municipal sludge compartment.

Once we have compacted it and brought it into this compartment, then, we take this compartment and spread it out on agricultural land. It's land where the cows graze and it is where we

raise our crops.

I read in a reassessment by the industry that Class B biosolids are not applied on soils or that the crops produced are not consumed by humans. This is incorrect, and I will be happy to provide further information later on.

[Slide.]

So, what we observed here is that the biocides have a quite long lifetime, and they transfer from the water back into the sludge, and then into the soils. The plants, they remove, but they do not degrade the chemical. These are wastewater treatment plants.

The biocides are transferred to the sludge and concentrations are 5 to 6 orders of magnitude higher. We did another prediction. Again, we predicted first that we have this chemical across the United States. People said it's probably not true. We have demonstrated now that this is true.

From the plant, we calculated the average usage of mass per person, extrapolated to the United States, and made a crude estimate, and this

is just what it is, a crude estimate of where these chemicals end up.

We estimate that 150,000 pounds of triclosan and 175,000 pounds of triclocarban are applied every year in sludge on agricultural fields used for either grazing or crop production.

Neither of these pesticides is approved or tested for agricultural use. They are both labeled pesticides, they are EPA registered as pesticides, but not for agricultural use. Nobody is looking for these chemicals right now in food.

Let's take a look at what happens in food.

[Slide.]

We had the methods. We began to study whether these chemicals are present in the food.

[Slide.]

First, I would like to make a point here. We can study a lot of things, and we can measure a lot of chemicals in the environment. Oftentimes it means nothing, because if something is there, like a heavy metal or something, unless you take it in, you get exposed, it's completely meaningless. The

chemical can be there, it doesn't make a difference. Don't be scared by chemistry. We are made up of chemistry.

The point here is that if there is something that is not good for you, and it gets to you, that's not good, and that's the stuff that we try to figure out in Public Health.

So, the question I am asking here, are people getting exposed unintentionally to these types of chemicals.

[Slide.]

In the literature, there is a rare account of two infant deaths. They were due to overdosing of disinfectant in a laundry in a hospital. The disinfectant used was made up primarily of chlorophenols, and these have again been removed from the market primarily.

[Slide.]

The chemical also contained or the mixture also contained 4 percent of triclocarban, so whether these deaths are linked to triclocarban or not cannot be said for sure, however, we do know

that triclocarban causes disease in humans. It causes methemoglobinemia, better known as the blue baby syndrome, so it's an inability of carrying oxygen.

So, there have been multiple cases, not only in the U.S., but also in Europe, and they forced the Committee on Drugs, in 1971, to publish the following recommendation, saying that clinical judgment would dictate avoiding even the most innocent-appearing substances in the nursery until data on toxicity are available.

I do believe that we still don't have the data that was asked for in 1971, and I encourage the funding agencies to make funds available to independent parties to conduct just this research to find out what these chemicals do.

[Slide.]

Human exposure to environmentally persistent biocides. We conclude that triclosan is detectable in drinking water resources. Triclocarban was detected by us in fruit juice, we have a study coming out. Triclosan has been

detected in fish. There is multiple reports by other laboratories.

There is one study of triclosan in breast milk. Again, this is the bioaccumulation process of once it's in fat, it doesn't leave it, and breast milk obviously has a high percentage of fat, about 4 percent, and we have made other detections of triclosan in breast milk.

Triclosan and triclocarban are detectable in human blood. The World Wildlife Fund has done a study, and we also have some data on triclocarban.

Finally, triclosan can be detected in human urine. What does that mean? It mean that we take it in constantly, and we also excrete it constantly. This is not the issue of bioaccumulation. This is that there is so much going around that we actually excrete it again.

The CDC, the Centers for Disease Control and Prevention at Atlanta has now begun to routinely screen urine and blood for the presence of triclosan and also triclocarban, and they found that 24 out of 30 people, representing the general

population, had detectable concentrations of triclosan in their urine.

[Slide.]

In summary, I think from the data I have presented today, it is evident that both triclosan and triclocarban, but not all the other, you know, biocides we discussed today, persist in the environment, that they are produced faster than they degrade, so what we are facing here is an unsustainable usage.

They contaminate sludge, a potentially valuable resource that has been used for many centuries or millennia as a fertilizer.

It contaminates the food supply. It bioaccumulates in fish, biota, and also in us, because it's detectable in human blood, milk, and urine.

Since it contaminates soil and aquatic sediments, I think we should take a closer look at the ecology of this. We heard before about microorganisms, the chances of development of antimicrobial resistance. Somebody said it's a

matter of size, and, you know, you wait long enough and you give it enough chances, eventually, it will happen.

What we are doing right now with the recycling of the sludge or the application of the municipal sludge is that we have a lot of pathogens in one place because we took them all out of the water, and then we take all the disinfectants out of the water, and we put them all in one plate and let them incubate.

We do this on a scale of 12.5 billion dry pounds of sludge per year. This is happening right now, and this is a big incubator that is being set up right now. Nobody is looking into whether this has any effect.

I think I gave you some evidence of potential or known risks that we need to consider when we judge the benefits and potential risks of these chemicals.

Thank you.

DR. WOOD: Thank you.

Let's move on to Mike Hartman.

EPA Regulatory Process for Antimicrobials

MR. HARTMAN: Good morning and thank you for giving me the opportunity to speak to you today

about EPA's regulatory processes around pesticides.

I am not sure if I am the only one that is hearing the radio.

DR. WOOD: Sorry, I looked into that. Apparently, according to the sound guy we are less than a mile from a radio station, and for that reason we are picking up the ads that are being beamed to us right now.

MR. HARTMAN: I am glad I wasn't the only one.

Again, my name is Mike Hartman. I am one of the managers in the Antimicrobials Program in the Office of Pesticide Programs in the Environmental Protection Agency, and I am going to talk to you today and give you a brief overview about the regulatory framework for the regulation of biocides in terms of their pesticidal uses.

[Slide.]

Again, the goals of our program are to

protect human health and the environment from potential pesticide risks, while at the same time ensuring that pesticide users have access to the appropriate tools they need in order to do their work.

[Slide.]

The main statutes that govern our program start with the Federal Insecticide, Fungicide and Rodenticide Act, which was most recently amended in 1988, FIFRA. This statute provides the main regulatory framework for all of the pesticide programs.

The Food Quality Protection Act of 1996, which radically impacted several aspects of the regulation of pesticides in the United States. The Federal Food, Drug and Cosmetic Act in terms of our setting of tolerances, and most recently, in 2004, the Pesticide Registration Improvement Act, or PRIA, which generally has impacts only in terms of scheduling, and those sorts of things.

[Slide.]

In its broadest sense, our regulatory

framework includes three main programs: the Registration Program, the Reregistration Program, and what we are calling the Registration Review Program. I will briefly describe each of those and how they work together.

[Slide.]

The Registration Program is the program in EPA which is the gateway to the marketplace for pesticides. Essentially, what we do in this program is to grant licenses which are necessary in order to use a pesticide in the United States.

These licenses can be granted under a number of circumstances, primarily for new active ingredients that have been developed as pesticides, for new uses of existing active ingredients, new products, and also for changing the way a product is used or amending a product.

In this program, our goal is to ensure that all new pesticides and new use patterns for existing pesticides do not pose a risk or concern to human health or the environment.

[Slide.]

The Pesticide Reregistration Program is a program we have in place at EPA, which ensures that older pesticides meet the current environmental and

safety standards.

The scope of this program includes all active ingredient pesticides that were registered prior to 1984. The goal in this case is to mitigate risks of concern for existing pesticides without disrupting unnecessarily agriculture, public health, or other vital uses.

[Slide.]

Finally, Registration Review is a program which is just coming out of its infancy. What it will provide is a 15-year review cycle for all pesticides, and the implementation for this new program is projected to begin in 2007.

[Slide.]

The general process in terms of how we review pesticides is basically the same for any of these programs. We go through a data collection phase. Once we have collected and analyzed the data, we conduct a risk assessment.

Once we have a risk assessment and understand the nature of the risk, we go through a risk management phase, and finally, ultimately, making a regulatory decision whether that is granting a new registration or changing the existing registrations.

[Slide.]

In terms of data, EPA has pretty broad authority under FIFRA to require data to support a registration. These data can include things like toxicity of the compound, product and residue chemistry data, data on ecological effects, environmental fate, exposure, and also efficacy, and this is efficacy in terms of whether or not the pesticide is killing what it is claiming to kill.

Also, it's standard practice in the agency, in dealing with pesticide reviews, we also will do literature searches of peer-reviewed data that is available, and take that into consideration when we do our risk assessments.

[Slide.]

In terms of risk assessments, under the

FIFRA framework, we have to consider a wide range of risks including risks resulting from residues in food, from occupational risks of actually handling and using the pesticides themselves.

Impacts on water resources, exposures in the residential setting, impacts on non-target terrestrial and aquatic organisms, and also, as a subset of that, we also have to look at endangered species.

The acceptable risk standard in most cases in the FIFRA framework is what is known as "unreasonable adverse effects." Essentially, what that means is that it is a risk-benefit weighing that is necessary under the FIFRA framework.

[Slide.]

In 1996, as I mentioned earlier, FQPA was passed and it did have some tremendous impacts on the way we regulate pesticides. First and foremost, it introduced a new safety standard, the "reasonable certainty of no harm" standard. Essentially, what that means is that we no longer have the risk-benefit weighing for certain use

patterns and certain exposure scenarios, primarily those dealing with the exposure to food, drinking water, or in residential settings.

Also, when FQPA was passed, we had to start doing some new types of risk assessments, as well. Now, we are required to do an aggregate exposure assessment. Essentially, what that means in our lexicon is that you have to look at all of the potential routes of exposure from particular pesticide primarily in terms of residues in food, residues in drinking water or in residential uses if they have them from the pesticide use.

We also have to look at cumulative effects of pesticides. What this means is if we identify several pesticides that have a common mechanism of toxicity, we have to consider the potential for exposure to those various pesticides and do a cumulative risk assessment for those.

The Act also required us to pay special attention in terms of the effects or potential effects or susceptibility to infants and children, and also requires us to undergo an endocrine

effects program. I note on this slide that that program is still in its early stages of development, however, all the other aspects of FQPA have been actively part of our day-to-day business now.

[Slide.]

Another thing that came about as a result of FQPA is the agency undertook a big step in terms of this public participation process especially around reregistration actions.

This public participation process is put in place to provide a framework for stakeholders and public involvement in reregistration. It offers a consistent, defined, predictable opportunity for those that are interested in these pesticides to have an opportunity to participate in the process, as well as giving us the flexibility to tailor the process to our particular needs in terms of a particular pesticide, in terms of its use and its risks. I am going to describe the public participation process very briefly for you.

[Slide.]

Again, I mentioned that we have an opportunity to tailor our approach. We have three basic ways of going about dealing with the public

process.

We have a six-phase approach, which is what we call our full process. We generally will only use this process in cases where we have very complex issues and risk concerns, and we expect that significant mitigation is likely to be required.

The four-phase process or modified process is the one that we will typically use or default to. This is where we don't have those circumstances that would require a six-phase process, but we still have an open public process, and also we have a low-risk option where we don't expect either to have any risk or any mitigation, and therefore we would have an truncated process in those cases.

[Slide.]

The public process itself, I am going to describe the four-phase process, which is the most

typical process. The first two phases involve an opportunity for the registrants and data doers to have an opportunity to look at the risk assessment and provide us with comments in terms of the errors that they may perceive in that document.

The intent here is just to make sure that we are not making any calculation errors or things of that nature, not an opportunity to discuss interpretation or endpoint discussions or things of that nature.

Following that opportunity, we will consider those error comments and make any changes we think are appropriate, and then release those risk assessments to the public via an FR notice and opening a docket for a public comment period.

[Slide.]

Phase 4 of the process begins the day that the public comment period ends. This is when we will review those public comments, make any revisions to the risk assessments we feel are necessary. If appropriate, look at developing some preliminary benefits characterization, and also

looking at risk reduction options if they are necessary.

This is all done in conjunction with other EPA offices including the Office of Water, Office of Solid Waste. We also consult other agencies, other stakeholders in the process of developing these risk management decisions.

[Slide.]

Those of you who may be interested in getting involved in these processes, we always encourage folks to get involved early and to utilize the schedules that are available online and our website to plan your opportunities for participation for those chemicals for which you have specific interest.

Again at the end, I will give our website, so you will be able to see where those schedules are.

[Slide.]

I will just use triclosan as an example, but I could talk about any number of biocides that are going through the reregistration program, but I

know triclosan was one of the major focuses of this meeting.

As a pesticide itself when it was first registered in 1969, and there are currently 22 registered products, our understanding is that probably about less than 5 percent of the total triclosan use in the United States is associated with the pesticide use.

There are several use patterns that have been approved including hard surface disinfection and sanitization, coatings, swimming pool water systems which for the life of me, I couldn't actually find a label that actually has it on there, so I am not sure if that's just a database anomaly. Also, materials preservatives, which is by far and large the biggest use of this chemical in terms of being used in textiles, plastics, and those sorts of things.

[Slide.]

In terms of the triclosan process specifically, we have tentatively set a reregistration decision date of late in the Fiscal

Year 2007. The data review and risk assessment development would begin late in 2006 to conform to this schedule.

Again, if there are other pesticides or biocides that people are interested in, there are a variety of schedules associated with these things. Quaternary compounds are going through reregistration currently, and we expect to see risk assessments on those becoming publicly available early next year with the decision on reregistration happening later next year.

[Slide.]

Again, this is just our website. This is where you can get a lot of information on the processes that I have just described, as well as specific schedules associated with the various pesticides going through reregistration.

Question and Answer Period

DR. WOOD: Thank you very much.

We have got a period assigned for questions and answers, and we have obviously heard a lot of material this morning, so it seemed to me

like it might be worth trying to organize the committee's questions into three broad topics. There may be others that you want to raise, but under efficacy and benefits, and a second topic of resistance, and the third one of environmental contaminants.

It would be helpful, I guess, if the speakers were available to answer specific questions that the committee might have to address to them.

Questions. Robert.

DR. TAYLOR: On the efficacy and benefits portion, I wanted some clarification on were there seasonal differences in the conduct of those studies. Have there ever been any relationship to results which seem to be quite variable and relate to season?

DR. OSBORNE: An example would be the Luby study from 2005, had a previous study a few years before that, that Dr. Aiello actually referred to in her presentation. That study did not show a statistically significant difference for

triclocarban soap versus placebo soap in reducing impetigo.

However, that study ended up not being powered sufficiently because Karachi, Pakistan, had the driest summer on record in the previous 40 years, and a pilot had told them how many households to put in the study, and it ended up being dry in the summer and not having impetigo.

So, seasonally, looking at impetigo in the summer is not a good time. You would have less of it in the summer, perhaps more in the fall or the spring where things would be wetter.

Another one of the studies mentioned that the March to May time frame was used for one of the school studies, and the authors indicated that that time frame might not be indicative of the whole illness category that they could have selected if they had different months.

For example, the one study had two groups that were analyzed for four weeks with a two-week washout, and if you looked at the total number of illnesses in control and intervention, the second

four-week period had about one-third fewer total infections than the first four-week period, and that would have been a time frame issue going from March to May. March is still in the cold and flu season, and May is much less.

So, there are differences depending upon what illness you want to study and what time of the year.

DR. TAYLOR: It seems to me that there ought to be some correlation to the actual rate of those diseases occurring historically to see if, in fact, the rate occurs during the study, so that you are not getting an artificial rate at the time you are doing your study.

DR. AIELLO: In general that we looked at, there was very little control of seasonality, so as you mentioned, they discussed the seasonality, but they don't control for it specifically as a variable.

The other issue is that if you are talking about differences, the differences are going to be experienced by both the intervention and the

control group, so, in general, you would see the biases in both arms of the study arms, so it wouldn't really impact as far as differences when you are comparing the intervention to the control group, it would be across the board and potential bias the results towards the null, or could even bias the results the opposite way, toward significance if they are looking at a period of time when there is higher rates of infection.

DR. TAYLOR: But if you do the study at a time when the rate is low, you may not see a signal.

DR. AIELLO: Exactly, you may not. That is what I am saying, it may bias it more towards the null, during times when there is less infection, so it would be much harder to detect a difference between the two groups, that is true.

DR. WOOD: Ruth.

DR. PARKER: I had a question about soap, and I wonder if you could tell me about what works about it, water versus an ingredient versus the mechanical, you know, water alone, water plus

whatever is in soap.

What do we really know about what works and what doesn't work, and also, specific to that, whether or not any of the soaps, some of which are labeled as having any microbial or antibacterial characteristics, are there any that have a residue on the other end of it.

I am just thinking sort of from the consumer perspective of trying to understand what these things do.

DR. WOOD: So, the question is, is the effect due to mechanical effect or a chemical effect.

DR. PARKER: Right.

DR. WOOD: Does somebody want to take that?

DR. ROGERS: I will take that. Soap has mechanical effects, but it may also have a surfactant effect, so washing with plain water, if you use some friction, will get some organisms off the skin.

I don't know that there is much data on

the differences between washing with plain water versus washing with regular soap, and as far as residues, I am not sure, that might be ingredient-specific for the different soaps.

DR. WOOD: But it would be fair to say from your data from your presentation, that the vast data in terms of efficacy were for soap alone, is that right?

DR. OSBORNE: The best data were for soap alone compared to not washing?

DR. WOOD: Right.

DR. OSBORNE: I believe that that is correct.

DR. SNODGRASS: One of the questions I had was are there data about efficacy in different socioeconomic groups or different household types of factors, for example, city water chlorinated versus unchlorinated rural water, that type of situation, as well as other maybe socioeconomic factors in terms of efficacy.

DR. AIELLO: Well, most of the studies as far as when I mentioned controlling for confounding

factors, most of the studies did try to control for socioeconomic status, so they tried to make sure that either the groups were comparable in socioeconomic status or they collected data on socioeconomic status.

But as you can imagine, it is often difficult, the measurements are very different, for example, if they are collecting data in less developed areas, it is not really clear whether the information, for example, the ownership of a refrigerator might be a characteristic of socioeconomic status. It is very variable across studies, but most of the studies have considered socioeconomic status as a factor that may impact results.

DR. SNODGRASS: So, the short answer is there is no difference?

DR. AIELLO: Is there differences with socioeconomic? We don't know, because very few of the studies have actually studied socioeconomic status as a factor, as a predictor of infections, for example.

DR. SNODGRASS: I guess the reason I am asking is one could reasonably expect more or less, take diarrhea. I am a pediatrician, so infants, in

some circumstances, rather than in other

circumstances, therefore, you might have greater

efficacy in one group compared to another group.

DR. AIELLO: Right, and that is what we

expect to see, but, you know, there hasn't been a

lot of studies that have measured what the actual

impact of socioeconomic status is. All the studies

do is control for these factors and rarely report what the effect estimates are for socioeconomic

status on infection rates.

DR. SNODGRASS: So, we don't have that

data.

DR. AIELLO: No, no, it's very important data actually.

DR. WOOD: Well, we sort of do, though. I

mean the data from Karachi was presumably a low

socioeconomic--

DR. AIELLO: Yes, across the board.

DR. WOOD: So, the absolute rates there

and the absolute reduction there was obviously different from the U.S., which would be a different socioeconomic class. What you are saying is there has not been within study socioeconomic stratification.

DR. AIELLO: Exactly, yes.

DR. WOOD: Any other questions? Yes.

DR. PATTEN: I am wondering if there are data to indicate how persistent, how long lasting handwashing education is once the research project is over. Do people continue to wash their hands in an educated fashion, or is it back to--

DR. AIELLO: This is an issue for intervention studies especially ones that take place in lesser developed countries, often, for example, with a water well that is put in. There is very little data on duration of interventions over time after the study leaves the area. So, there is very few follow-up studies in general on even public health infrastructure improvements.

So, you know, for hygiene, that is the case where the studies go in, they do the research,

and then often they leave right afterwards and we don't have follow-up information. Whether people keep up with these hygiene practices is really unknown at this time.

DR. OSBORNE: On the Larson trial, the investigators contacted the households weekly, so that gives you an idea that they felt that they need to keep a presence weekly in order to maintain what they had set up in that study. They visited monthly and quarterly, as well.

DR. PATTEN: For how long a period of time?

DR. OSBORNE: That was a 48- to 52-week study.

DR. AIELLO: Right. It's only over the study duration, though, they are doing the follow-up. They didn't follow up after the study period.

DR. WOOD: Getting back to Sonia's question, that was really a reinforcement intervention rather than a follow-up to see whether there was voluntary effect.

DR. PATTEN: I think this is an interesting question given what we are now told about healthcare professionals and their

handwashing habits in their work settings, that their education does not persist.

So, I wonder what we can expect from a general population.

DR. AIELLO: I don't know how we are going to have in-services in the community. It's a little bit difficult to do.

DR. WOOD: Terry.

DR. BLASCHKE: Given the limitations of the studies that you described with the alcohol-based handwashes, I am just wondering if there is any information that really compares the alcohol-based handwashes versus the antibacterial soaps and whether it is controlled or observational.

DR. AIELLO: We didn't come across any in our literature search comparing between those different arms.

DR. WOOD: Jack.

DR. FINCHAM: I don't know if this fits in the framework of the questions that you outlined, but I had a question for Rolf about the biocides.

In the presentation, several of your slides you noted a pregnant woman with a child in utero, and I just wonder, your impression of

exposure in the CSF or across the placental barrier, or anything like that?

DR. HALDEN: That is an excellent question. I think we are always concerned about the most susceptible population. Obviously, the developing fetus is probably the most susceptible of a human being we can think of.

So, we have generated a repository of 300 core blood samples with corresponding umbilical cords, and we are analyzing them right now. I, unfortunately, can't give you any data yet, so I can't say yes or no, but I will be able to do that in a few months, so the answer is we don't know right now, we will find out soon.

From the chemistry, I think we can predict that the chemical crosses the placental barrier,

and if it has any endocrine disrupting effects,

then, this would be the place to find it.

DR. WOOD: Mary.

DR. TINETTI: It is okay to ask a question

about resistance?

DR. WOOD: Sure.

DR. TINETTI: It would seem a pretty

easily testable hypothesis in a real world setting to see what, if any, degree of resistant organisms

develop with the use of these things.

We have heard a lot about theory, we have

heard a lot about in a laboratory environment, but

I am just sort of curious why Larson or Luby and some of these others hadn't incorporated just

testing the cases and controls in their studies,

and is there any push towards actually looking for

real world evidence of resistance with the use of

these products.

DR. WOOD: Dr. Levy, do you want to

respond to that?

DR. LEVY: We were part of the Larson

study with Allison Aiello, and we did look at the

law of gram positive and gram negatives, and as I demonstrated, we saw what was a surprising lot of antibiotic-resistant bacteria already there, and the question was where did it come from.

So, you are starting at a high level, and so the question then comes now you add on top of that, the antibacterial and non-antibacterial, and do you see a difference, and we didn't see a statistical difference although we saw, in the population, these bacteria groups that were skewed toward resistance to or less susceptibility to triclosan, which raised the question why and will it not get worse.

I think that in my experience with antibiotics, a year is not enough, and I think it has to be followed, and secondly, in the laboratory, you have got everything controlled and beautiful, so it can happen, you know, in one-year time.

DR. WOOD: Before you go away, I mean when I look at that slide, your slide, it looks like about 30 percent, 40 percent, I guess, of the

background organisms were already resistant. So, I guess based on that, would you expect to see a change?

I mean if the assumption is previous exposure over years has produced that resistance, would a short-term study like the Larson study produce further resistance, so you would see?

DR. LEVY: Given the story with antibiotic, where we have, for instance, E. coli now among all of you, is probably going to be about 30 percent resistant to ampicillin and tetracycline if I looked at your E. coli.

If I gave you a load of an ampicillin or something and then tested you, fine, but over the normal course of different people in the household using it, no, you wouldn't see it.

So, that's one of the problems with that kind of study, and a study that we are now putting together where we just did a random sampling of homes that did or did not use antibacterial-containing products, and the problem we had was that there were virtually, out of 38

homes, maybe 1 in which we could find that kitchen and bathrooms did not have it.

Otherwise, we had to separate it, look at the kitchens alone and the bathrooms alone, because by then, there had been such a plethora of these products that we couldn't do it.

I made my message. I think that a year is too short. I think that one needs longer studies and then the question comes up should we have to wait for those studies.

DR. WOOD: Let me return to the question. Is it your conclusion or your thought that the resistance that you saw in the background setting was at least contributed to by exposure to these compounds? Is that the take-home message?

DR. LEVY: No, we could not say that, because if we look at the users and the non-users, we saw the same high background.

DR. WOOD: But based on what we had from the environmental contamination.

DR. LEVY: My study can only--our study can only say that users and non-users, we saw

resistance to antibiotics and the skewing of less susceptibility to the biocides in all the homes. We just didn't expect it, and so that was not something we could have predicted early on.

This is, of course, a population which Dr. Larson later showed has access to antibiotics, have access to other products, so while it was a nice, an absolutely marvelous study, the question is was it the right study for looking at what you are asking, which is start with an antibacterial soap and not, and you start at a low level, what happens.

DR. WOOD: John.

DR. POWERS: I am John Powers. I am the lead medical officer for antimicrobial resistance initiatives at FDA.

I just wanted to make a comment about the often stated that this should be an easy hypothesis to test, and frankly, it is not. It is not even testable and I think for a lot of the reasons that Dr. Levy is bringing up, if we just look at issues. There is something to do with particular drug

organism combinations. Penicillin has been around since 1941, wouldn't find a drug as widely used as that ever, and yet Group A streptococci in people's throats have yet to develop resistance, drugs used all the time.

It took 40 years for vancomycin resistance to develop in enterococci, and yet we saw a rather rapid, over time, resistance with fluoroquinolones and E. coli even though you couldn't select for it in the lab.

So, the question is what experiment do you do to actually try to find this, and there is a great adage I always like that says, "Absence of evidence is not evidence of absence," and that's what we are with here.

If you don't find something, does that mean it is not going to occur, and as Dr. Levy so eloquently put, in this setting, all of the historical evidence would argue that's not the case, that it is going to occur over time.

DR. SNODGRASS: I wanted to pursue this a little bit more. In looking at this slide, this 40

percent resistance, are there indigenous populations or other populations where there are historical information, you know the resistance should be less than 1 percent as an example?

DR. LEVY: As you probably can guess, there have been very little studies looking at susceptibility to these products. In the limited one that I think there is one that we looked at, just home, not with or without, there was not a remark on resistance in some of the antibiotics we tested.

So, as I said, we were surprised, just as in 1979, when I tested the fecal flora of medical students at my university and at Harvard, they looked the same, and they were heavily with resistant E. coli, and no one expected it, because they were ambulatory populations, and it just had happened over time, whereas, the previous data came from the decade before in which all the resistance was in hospital patients.

So, there is this time element and volume which is going to make a difference, and if your

bacteria doesn't know that you are using triclosan, and not penicillin, I mean lets face it, I mean if they are going to survive, they are going to survive.

DR. BLASCHKE: I have two questions for Dr. Levy.

You talked mostly about the biocides, the triclosan and triclocarban. Do you want to say anything about again alcohol-based biocides in terms of resistance?

DR. LEVY: If you take E. coli, for instance, and put it in a very, very small, 1 percent alcohol, and then gradually increase it, you can get what is called kind of a tolerance to it.

I mean how you are ever going to test it, I mean you can't an MIC on a plate, but it is hardly one, which it's in a growing situation, it is not in a situation where the bacteria are resistant to the drying activity, which is what is the basis of the alcohol activity.

So, I have never seen anything in

resistance. It's a sort of, you know, it is a different way of dealing with the bacterium. It is not stopping a process, it is actually, in my mind, drying it up, removing water, and I think that in this, rapidly, not in the case as we do when we lyophilize.

So, we don't concern ourselves with alcohol resistance, peroxide resistance, bleach, because of what I mentioned, the residue. Bacteria needs some time to, you know, they have got to get 100 million there or even 10 million to be able to select out the one that is going to take over.

DR. BLASCHKE: And on a different thing, a follow-up. Are the resistant organisms, do they revert to wild-type, is there a loss of resistance with time? Is there any data to look at that in bacteria?

DR. LEVY: I can only speak from the standpoint of antibiotic resistance, and there is not loss, there is replacement. When the Finnish Medical Societies removed macrolides from their first choice or second choice for the treatment of

Strep pyogenes because they saw such a mounting resistance, the question was are they going to lose the resistance determinant or not, and it turns out the strains just got replaced.

It is sort of like the answer to the contamination is dilution, and I think that what happens is that the resistant strains did not have an advantage, and the susceptible came back, but they weren't of the same type, so they could tell they were not losing the resistance.

The bottom line is when you create a resistant bacterium, often it is a genetic event which is nonreversible, so your best bet in getting a susceptible is for a replacement, and that is why the movement forward, if we look even at some our intestinal studies where you gave the person tetracycline for three or four days, you see a rapid change in the fecal flora, and then you stop the tetracycline.

You might have had the resistance emergence in two or three days, but to get back to the level might take two weeks, because there is

nothing intrinsically growing, or shall we say selecting against the resistant organism, so it's a rapid selection.

DR. CLYBURN: I have a toxicity question for Dr. Halden.

I was just curious, it did go against some of the things in our packet. I wanted you to clarify for a second about the use of sludge and agricultural uses.

DR. HALDEN: Municipal sludge, also called biosolids, can be classified as Class A and Class B. This classification is done exclusively on the pathogen content. We are concerned about that microorganisms are carried over onto agricultural crops.

There is Class A biosolids are the ones that are more clean and considered useful for a lot of applications. If you go to a store, to any hardware store, and pick up some fertilizer, you can pick up a bag, and it contains, it will say on the label it was made up of municipal sludge, but it has been heat treated such that there is no

organisms in there.

The Class B biosolids are specifically designed also for land application, but since they have a higher pathogen content, they have much stronger, more stringent rules, so you can't just, for example, put sludge on a field and then grow tomatoes. You can't grow a crop that is in touch with the soil and potentially can pick up the microorganism.

What you can do is you can go to the supermarket today and buy sweet corn that has been grown on Class B land applied sludge. Why is that? Because the corn plant emerges from the soil, grows up 5, 6 feet tall, and then you have development of your corn plant that you actually buy, so it is assumed that there is no contact between the corn and the sludge.

It is a difficult issue to assess exactly what you can grow. There is many regulations there, but it is wrong to say that Class B biosolids are not used in agriculture. They certainly are. The whole class was designed for

the purpose of making sure that they are supplied in agriculture, but in a safe way.

I guess that answers the question, I hope.

DR. PARKER: I had a question for you, as well, about CDC's collection and analysis of the triclosan in urine, and the date you noted was just 2005, sort of a recent.

You noted the increase in publications and the plethora of publications about it, but I wonder if you could give a little historical context to that measurement, why they are doing it now, as well as what they knew about those where it's present versus those that don't have it in their urine. Do we have any further information about it?

DR. HALDEN: There was a paper coming out in Analytical Chemistry. I have it with me, so you can take a look at it. It was a methods paper, so it describes how these things can be measured using an automated system.

They used 30 individuals representing non-occupationally exposed persons from the general

population, found it in 24 or 30 individuals. They also looked at other phenolic compounds and found a number of those at low levels.

Why is the CDC looking at these chemicals right now? I think because triclosan has certainly made a lot of waves recently with the formation of chloroform when it is combined with chlorinated water.

Chloroform is a probable human carcinogen. Then, the formation of 2,8-dichlorodibenzoparadioxin, and I think dioxins are something that really scares the public, so that is always an issue that then is followed up on.

With respect to triclocarban, the CDC really started after we introduced our paper in 2004, and we are collaborating with the core blood repository with other investigators at the Johns Hopkins University including some clinicians.

So, we have kind of spread the word that this chemical was all that we were actually presenting at the CDC, too, and so they included

this chemical into their suite of compounds that they are looking for now.

DR. WOOD: You have mentioned dioxins once or twice. Is that a realistic hazard from this, are the concentrations really at levels that people should be worried about, or is it just that people are emotive about that?

DR. HALDEN: I think there is two different levels, we have to look at the two sides. First, we have to look at environmental concentrations. I think if the concentrations we find are in the nanogram per liter, low nanogram per liter range, these are very, very low concentrations. They might be an indicator that we can follow a process. I personally don't believe that there is a huge human health risk if your drinking water, for example, contains very low levels in the nanograms per liter.

Then, there is the issue of finding much higher concentrations in the soil. Now, we are talking milligrams per kilograms, so that is 6 orders of magnitude more. That is certainly a

concentration that makes a difference.

If you look at the measurements of the actual exposure of human beings, I think if we can detect on a routine basis, compounds like triclosan in urine, that tells us that there must be a steady influx of these chemicals into the body, I don't know what the usage rate is for the general population in terms of antimicrobial products, but I do know that a lot of people who say they don't use it, actually do use them, because they all go to restaurants, they all have their children in the preschool, and they use the facilities, and so forth, and a lot of these facilities contain these chemicals.

So, I think the exposure might be much broader than we know. I think a lot of people might get exposed to these chemicals that don't expect to be exposed, and the CDC is now producing the data, providing evidence for this.

DR. BLASCHKE: As a follow-up to that question, have there been any tissue assays done, fat biopsies or anything like that in humans?

DR. HALDEN: I haven't done any, but if anybody is willing to expend some research dollars, you know, I will be happy to do these studies.

DR. TAYLOR: Could you summarize the risk assessment studies on these compounds, have there been the risk assessment, for example, what is the NOEL?

DR. HALDEN: Yes, the question is regarding the levels that we find in the environment, how do they relate to the actual risk. Typically, we are concerned about the health of aquatic biota. A lot of people think that these chemicals get into the water and then potentially harm the microorganisms or algae, for example.

Algae are the most susceptible organisms to these types of chemicals. The concentrations that we find in many samples are below the level. The concentrations that we reported with triclocarban were certainly much higher than the levels, and there was a dispute in the literature, you can follow it in Science and Technology, whether the levels that we found, whether they are

important or not.

An argument was made that the industry has higher confidence in what they predict to be present in the environment. There is stances that I have more confidence in judging the concentration that actually are present in the environment.

What we definitely need is more data, so to answer your question specifically, I think we have examples of concentrations that exceed the no effect level, and we have examples of concentrations being below there.

That is all we know right now.

DR. WOOD: Mary.

DR. TINETTI: I have a question--this is for probably somebody from the FDA--about the persistence. We are sort of hearing, on the one hand, persistence is a good thing, because if you keep it on there, you are going to keep the microbial count down. On the other hand, persistence is going to lead to a greater likelihood of resistance.

I guess I would like to hear--it makes

sense in a hospital healthcare setting that persistence is an issue, but if what you want to do is just get rid of what is there immediately, what role does really theoretically persistence play in a non-healthcare setting, and why does that standard exist.

MS. LUMPKINS: Historically, there is a couple of things that tend to get confused, persistence versus cumulative. When we framed the consumer products in the '94 TFM, we were thinking that they should be along the same lines as the healthcare professional, and that was pretty much as far as our thought process goes.

When the panel, there is another concept called cumulative effect, which a lot of these antimicrobials have, which the panel theorized it would be a good thing to have carriage of these antimicrobials to keep in transient from becoming established as part of the residence.

So, I don't think at the time a lot of thought was given to persistence for the consumers. We were just looking around for an effectiveness

criteria that we thought would be workable.

DR. WOOD: So, that is something we should come back to probably.

Any other questions?

DR. SNODGRASS: I just have a comment on perspective of bioaccumulation of body fat in humans. In the late '70s, there was a National Adipose Tissue Study that was done on cadavers, I believe the NIH, on probably several hundred cadavers.

At that time, there was at least of the kinds of compounds they looked at, a lot of chlorinated hydrocarbons manmade, there was at least a dozen and a half that were low parts per billion types of levels, and I don't think anybody was saying that really was changing their risk for cancer, for example, in the lifetime of exposure, but everybody has it, newborns, what have you, those are known.

DR. HALDEN: I would like to comment on this. I think a lot of these studies go back. I think a lot of the chemicals that were detected

back then have been removed from the market right now. There is a real concern about persistence and accumulation of halogenated aromatics still in the environment.

If you look at the Safe Water Act, and look down the list of chemicals that are regulated right now by the EPA, you will notice that about two-thirds of them are chlorinated chemicals. I think if you look for a troublemaker, this is a good way you have to look first if you want to have success.

DR. WOOD: Robert.

DR. TAYLOR: Just out of curiosity, have these compounds been studied in the National Toxicology Program, NIHS?

DR. HALDEN: I can speak mostly for triclocarban, because that is really where I spend my attention. I have to say that most of the data that is available on triclocarban has been produced by the industry and has been safeguarded, so to speak, by the industry for several decades until they were forced by the EPA, through the high

production volume and chemical challenge program in 2002, to release the report.

When that report came out, they had to show all the data that they had in terms of environmental--and by reading through this report, it was evident that this chemical is quite widespread, and so begin our studies.

To my knowledge, there hasn't been any studies done by the NIHS specifically to examine this. I think there is good concern, there is good reason to do this especially with the link to chloroanilines, which are certainly important because they are under review right now in the European Union called 4-chloroaniline and 3,4-dichloroaniline as known carcinogens, so there is an issue that might be much broader than the triclocarban itself.

DR. WOOD: Unless someone has a very, very pressing question, let's move on to the next speaker, who is Elizabeth Anderson.

Introduction

MS. ANDERSON: Thank you for having us

here today.

My name is Betsy Anderson and I am the Associate General Counsel at the Cosmetic, Toiletry, and Fragrance Association, CTFA.

Today, I am speaking on behalf of both my association and the Soap and Detergent Association, SDA. Together, we represent the manufacturers of products that protect the health of people throughout the world.

There are a number of issues that we will get into during the next hour, and I will be brief in my opening remarks, but I do think it is important to tell you in very clear terms that we believe there is an important role for topical, over-the-counter, antibacterial products in the lives of consumers.

As indicated in our submission, research demonstrates that consumer topical antimicrobial products render higher levels of bacterial reduction on the skin than those without an active ingredient.

Infection control increasingly takes place

outside of professional settings, in the home, school, child care, and community. When infection control is needed, efficacious products should be available to the consumer.

They help protect consumers in high-risk areas in the home including the bathroom and kitchen. They can control the spread of germs associated with activities, such is diapering and food preparation. They can make germ-rich environments outside of the home, such a daycare centers, extended care facilities, or public bathrooms safer, and they can provide important protection when caring for oneself or a sick family member at home.

The importance of controlling bacteria in the home is no different than in the professional setting. Consumers handle food, change diapers, deal with illness, send their kids to daycare, visit public bathrooms, and in so doing, face great potential for the transmission of pathogens to oneself or to others.

We believe consumers should be assured

that the products they are using are the most effective available. As our NDAC briefing document states, manufacturers of topical OTC antibacterial products support requiring consumer products to meet the same efficacy standard as professional products as long as an appropriate standardized method of testing is used by the FDA.

Effective antibacterial products control the risks associated with exposure to potentially pathogenic organisms, and are therefore appropriate and beneficial in a wide variety of nonprofessional settings.

Of course, effectiveness doesn't matter if safety cannot first be assured. We take the question of bacterial resistance seriously and are committed to continued research and active monitoring in this area.

Researchers have spent a great deal of time focused on the issue of bacterial resistance. A study published earlier this year by Dr. Larson found no evidence of bacterial resistance related to the use of triclosan in household settings.

This author is not alone in this conclusion. There is simply no clinical real-world evidence of increased resistance under current use conditions of topical antibacterial products.

We also take seriously the environmental impact of common antibacterial active ingredients, such as triclosan and triclocarban. This issue has been studied extensively, concluding that environmental impacts are unlikely.

Given the valuable role that topical OTC antimicrobial products can play in a wide variety of nonprofessional situations in and out of the home, and given the wealth of research supporting the efficacy and safety of these products, we feel strongly that consumers must continue to have the choice to use these products.

To shed more light on the important role of antimicrobial products in the lives of consumers, we have invited a number of distinguished professionals to speak today. They will confirm in detail the safety of these products, discuss the importance of infection

control in the home, review the benefits of antimicrobial products, and conclude with a discussion of the support these products have generated.

In the interest of time, we ask that the panel hold all questions until the end of our presentation. Also, I would like to add one final request. As you are aware, this meeting is being held without an industry representative on the panel as is customary.

Given this unusual situation, we respectfully ask that George Fischler, who is Manager of Microbiology with the Dial Corporation and sitting in the audience be allowed to serve as a point person for questions related to the industry's presentation.

We look forward to an engaging and informative discussion. Thank you.
Professor Gilbert.

Laboratory Studies: Resistance/Cross-resistance Development in Microcosm Communities

DR. GILBERT: Good morning. I am Peter

Gilbert. I hold a Chair in Microbial Physiology at the University of Manchester in England.

What I would like to do today is to share with you the results of some laboratory studies that we have been conducting at Manchester over the last five to six years.

What we have been looking at are the impacts particularly of additives in consumer products on complex bacterial microcosms.

[Slide.]

A little bit of background. In the real world, bacteria do not grow as monocultures. In the real world, bacteria live in communities which are very polymicrobial, on surfaces and in wet environments, you will find several hundred different types of bacteria and species growing together in cooperation.

That is certainly the case on the skin, on the gut, in the mouth, and in our general environment. Now, the bacteria within these communities do actually cooperate with one another, so if you impact on one, you impact on the whole

community.

Also, within those biofilm communities, we have both phenotypic and clonal heterogeneity. Often, the populations are extremely large, we have billions of microorganisms present within a very, very dense population, and the opportunity therefore for selection of the occasional mutant is very, very high.

So, we came at this problem very much interested in bacteria growing as communities.

[Slide.]

We wanted to go for a realistic challenge, and ultimately, most antibacterials that enter the home leave down the sink, so we had the task of setting up a simulation of a sink drain system.

The picture to the left actually gives you an indication as to the technology associated here. We have a constant depth film fermenter. We have a rotating pan, which is scraped by teflon scraper, and biofilms are formed in this that are about a half a centimeter thick. So, we are generating very, very thick biofilm communities.

We actually inoculated this model system with biofilm that was extracted from my home. It was extracted from a kitchen drain. It was taken

from a household that did not use antibacterial products since the actual plumbing had been put in place, so we started off with a very naive baseline community.

It was established in the lab in kind of rather novel way. We fed the biofilms four times a day. We were estimating that was the number of times that dishes might be washed in the house or a sink might be used to wash hands, so it was fed times a day with a synthetic dishwater, and the rest of the time, the whole system was simply kept moist. I like to think of that as a sort of dripping plant syndrome.

Initially, we established the community for a six-month period to get to a quasi-steady state, but then we initiated a four-year study where throughout that time we were monitoring the various bacteria that were present within that community.

We were looking not just for those bugs that we could grow, but we were also looking for non-culturable bacteria, and we were detecting them by doing DNA profiles.

Throughout that four-year period, all culturable isolates were collected, they were

archived. They were subject to 16S ribosomal sequencing in order to identify them, and particular isolates were actually tracked through the study using ribotying to confirm that they actually had the same origin.

The study included susceptibility testing to a wide range of biocides and antibiotics.

The studies of import related to dosing of these fermenters, which were able to be replicated, dosing of these fermenters for various lengths of time with triclosan-containing detergents and QAC-based detergents.

The dosing period for each level of these products was for six months, but I emphasize the whole study ran over a four-year period, so it is a fairly sustained exposure.

[Slide.]

This might look very hazy to you, but essentially, it's a family tree. We are looking here at the dominance of different microorganisms within the baseline community, and the family tree essentially depicts the relatedness between one organism and another.

So, what we see here is a baseline, very complex community. It consists of about log 11

microorganisms per gram. This is dominated by pseudomonads and enterics and bacilli, but it also contain things like sulphate-reducing bacteria.

Let's look at one of these. Here, we are exposing the Palmolive washing out liquid, three months at 4 MIC level, 3 further months at 8 MIC level.

During that time, what we actually saw was the community you have depicted here became less diverse. Essentially, organisms were lost from the system. This actually, in our feeling, corresponds to clonal expansion of pre-existing strains. So, the strains that now dominate this less diverse

community were there in the first instance. We were able to track them right back to the naive community we started with.

Having tracked them, we were able then to demonstrate that they had exactly the same antibiotic and biocide susceptibilities as they had before we started. All we have done was biased the community, so that it became clonally expanded with pre-existing strains.

Now, as Stuart Levy has intimated, the majority of the pre-existing strains that we see in a drain community are coincidentally insusceptible to many antibiotics and biocides. The ones that respond tend to be those that we find associated with disease. So, this sort of environment is dominated by organisms that are insusceptible anyway.

The little panel here shows two of the organisms that became very much clonally expanded in this drain community, and together those organisms can actually produce a surfactant that dissolves triclosan, and the second organism in the

pairing of this Alcaligenes xylosoxydans can actually degrade triclosan.

So, we generated a triclosan-degrading community within our mobile system.

For fun, we took some of the laboratory-trained triclosan-resistant E. coli's and deliberately spiked these into our drain system in the presence of triclosan to examine their survival of persistence.

In those studies, we actually found those triclosan-tolerant E. coli actually disappeared within three to four days of having been spiked in. So, it was really a very fierce competitive environment in which they couldn't survive.

[Slide.]

So, to emphasize, we are archiving the strains from the study over four years. We have done a retrospective analysis of susceptibility, and the culturable isolates have remain unchanged throughout.

[Slide.]

We have gone through a different approach

here. We have got a panel of 40 environmental and skin, environmental and human isolates of bacteria. Most of these are dominated by skin microorganisms, but we also included a range of gram-negatives.

So, these 40 ex-situ, fresh isolates were subjected to exactly the same sort of laboratory training that, with E. coli, leads to triclosan-insensitive strains.

What we found surprised us, because of those 40 strains, 35 of them remain totally unchanged in terms of their triclosan susceptibility or in terms of antibody susceptibility.

Only 4 strains could actually be selected towards changes in triclosan susceptibility. Two were E. coli, which we know responds, and the others were a Klebsiella, an Aranicola, and a Stenotrophomonas. Those latter 3 organisms are already so insensitive to triclosan that the small change we saw wouldn't affect outcome anyway.

So, we actually believe that selection for insensitivity to triclosan is not as widespread as

we might believe, but probably is confined to a narrow group of enteric microorganisms.

[Slide.]

So, what we are showing is that we think natural communities are fiercely competitive. If one organism is eliminated, its place is taken by another, or another organism comes into dominance as it becomes clonally expanded.

Exposure to antibacterials in our communities leads to clonal expansion of pre-existing insensitive strains. We see no evidence of emergence of de novo resistance traits, and lab-selected mutants incur a fitness cost and can't survive.

[Slide.]

With Stuart Levy's talk earlier on, I can't resist putting this slide up. Stuart introduced the concept of multi-drug efflux pumps conferring multiple antibiotic resistance. I have always referred to them by a slightly different term.

I like to think of these as an emetic

response in bacteria. It's the microbial vomit reflex in that when they are tickled with noxious substances, which would include biocides and antibiotics, then, they upregulate or express efflux and get rid of the material.

We did a study, which was published last year, where I sent one of my graduate students to a supermarket, and I got them to pick almost at random off the shelves 53 household products. Three of those turned out to be alcohol, which he drank and didn't actually do the study on, but essentially, we had a rather simple assay system here.

We would cut a well in a petri dish. We would place the product in the well. If there was an antibacterial there that induced efflux, then, you might see a zone of inhibition, as you see on the top left, a zone where growth is inhibited, but where efflux has been induced through mar, we end up with this sort of blue ring, and that is brought about by a reporter gene that has been incorporated in that strain.

What surprises was more than half of those 50 products were potential inducers of mar. What I haven't told you is that we had deliberately told

the student to avoid products containing antibacterials.

The products that induced mar operon tended to be spicy foods, things with ginger, garlic, because we forget sometimes that there are many, many natural substances out there in the world that form part of our diet, that bacteria have to contend with, as well as the actives that we are developing.

So, we found that the majority of the herbs and spices we use to preserve and spark up our food also induce efflux. I would suggest if you worry about efflux as a problem associated with triclosan and similar products, then, you also think about putting a moratorium on spicy food. I will end.

DR. WOOD: We will go on to the next speaker.

Environmental Safety of Active Pharmaceutical Ingredients

DR. REISS: Hi. I am Rick Reiss from the consulting firm Sciences International in Alexandria, Virginia. I specialize in risk assessment, ecological risk assessment, and a couple of years ago I published a study, An Aquatic

Risk Assessment of Triclosan.

[Slide.]

My talk is going to focus on triclosan and triclocarban, TCS and TCC, and for each chemical, I am going to review the general environmental fate characteristics of the chemicals, some representative environmental concentration data, the toxicity levels for the most sensitive ecological species, and a comparison of concentrations and toxicity levels, sort of a simple risk assessment.

[Slide.]

The general environmental fate properties of these chemicals, both have very similar properties. Both have very low vapor pressure, and that should say low solubility in water, but they

are soluble enough that you would see PBB level concentrations in the environment.

They are highly absorbent to organic matter. Both of these compounds will reach the environment through down-the-drain disposal, but in the next slide, I will show that both show significant degradation in water treatment plants.

We actually have a good deal of environmental degradation data on some of these compounds. For example, for triclosan, there is 2 die-away studies. These are basically studies where you would look at the concentration coming out of a wastewater treatment plant and then following that downstream to see how it reduces as it goes downstream, and those studies have shown a very rapid, 2 to 5 hour half-life.

There is also soil biodegradation half-lifes of about 17 to 35 days in 3 soils.

For TCC, we have a study that shows rapid degradation in biosolids with about a 10-hour half-life.

[Slide.]

This slide shows average removal rates in wastewater treatment plants, and this is in the water phase, so it is comparing the influent and

the effluent. Activated sludge are the most common plants in the U.S., and you see 94, 95 percent reduction in concentration.

For trickling filters, they are less common. You see a little bit less degradation, 77 to 83 percent, and the predominant pathway has been shown to be biodegradation.

[Slide.]

Let's look at some of the measured and modeled concentrations that are out there for TCC. First, some measurements that were done in the '70s and '80s, and compiled by the TCC Consortium, showed a maximum concentration of 0.23 parts per billion, and 90 percent of those concentrations were below 0.05 parts per billion in that collection of studies in mostly rivers in the U.S.

Dr. Halden has measured a maximum concentration, at least in his published work, of 6.8 parts per billion in sites with significant raw

sewage. I would submit that while that is a relatively high concentration, the problem of raw sewage is I think much broader than triclosan and triclocarban.

A lot of these studies, they go to look for the most vulnerable sites where you would see the highest concentrations, and that is important obviously, but we also like to look at something more representative, and at the moment, with the measurement data we have out there, the best thing to do is to look at an EPA model called E-FAST, and EPA uses this for regulating chemicals.

The model estimates show a high-end value at an outfall, maybe a 95th percentile, something like that, of about 0.017 parts per billion with the E-FAST model, and then the median level at about 13 parts per trillion, so much lower median concentration.

[Slide.]

For triclosan, what do we have out there? The United States Geological Survey has done a couple of studies, and they have published in the

last several years that have received a lot of attention.

In the USGS study in 2002, they were looking at locations that were considered again susceptible to contamination. They found a 95th percentile of 0.2 parts per billion and a median concentration of 0.14 parts per billion.

They didn't give a lot of information in that study about the particular conditions of the streams they were measuring, so in 2004, there was an additional study that divided the measurements into basically the flow conditions in the river, and when I say "low flow," this is typically what the USGS defines as the 7-day average flow rate in a river, the lowest one over the period of 10 years.

So, this would be sort of if you had a wastewater effluent during that low flow condition, that would be kind of a worst case condition in 10 years that you would have at that particular effluent location.

Triclosan was non-detectable in all of the

typical flow conditions, and it had a maximum concentration of 0.14 in the low flow conditions.

[Slide.]

So, we want to eventually put those numbers in context, so we need to look at what are the NOECs or the No Observed Effect Concentrations that are measured in the ecological toxicity studies.

So, these are all chronic values, and we are looking first at triclocarban in Ceriodaphnia. We have a NOEC, no effect concentration of 1.5 parts per billion, and in algae, we have a 6 part per billion, and that is a minimum algistatic concentration.

For triclosan, in blue-green algae, we have a NOEC of 0.5 parts per billion, and again that is algistatic, not algicidal, so it's reducing growth rates, but it is not fatal, and you see a recovery after the removal of the exposure of the population in about 3 to 6 days.

Waterflea, again, Ceriodaphnia for triclosan, you have a NOEC of about 6 parts per

billion.

[Slide.]

So, let's look at for comparing those NOECs to environmental concentrations for TCC. We see the NOEC in green of 1.5 for Ceriodaphnia. The maximum measured concentration in the TCC Consortium measurements was 0.23, so it's pretty far away from that NOEC level.

The 90 percent level was even lower, and the modeling values that we see were substantially lower than the NOEC concentration.

[Slide.]

Again, for triclosan, I put two of them up here. We have the NOEC for invertebrates of 6, and a NOEC for algae of 0.5, and then the USGS measurements are summarized there, and you see they are generally lower, significantly lower than the NOECs for invertebrates, and lower than the NOEC for algae, but there are measurements at the high end where they would equal or exceed the NOEC for algae, and that was essentially what I concluded in the risk assessment paper I wrote for triclosan

that you would see under worst case conditions, some algistatic effects as a result of triclosan exposure.

[Slide.]

Given the time constraint, I am only going to talk very briefly about terrestrial risk. It has been said both triclosan and triclocarban can be present in sewage sludge in small concentrations, I think ppm level concentrations.

The sludge may be used as soil amendments in agriculture, but there is a very low potential for ecological species, a low potential for exposure, and I am actually writing a paper that tries to quantify those exposures.

Also, there is an extensive database for these chemicals on mammalian toxicity, both acute, chronic, subchronic, and reproduction studies, and it shows a low mammalian toxicity. Again, the sludge concentrations ppm level. There is really a low potential for exposure to ecological species through this pathway, so it has been concluded that the risks to ecological species would be minimal

through terrestrial pathways.

[Slide.]

So, I will summarize the conclusions. The large majority of TCC and TCS mass will degrade in treatment plants, but some will be present in effluent and sludge. Neither is expected to persist in the environment given the die-away studies we had, given the biodegradation levels in soil and sludge that we have.

TCC shows low risk to aquatic species when high-end concentrations are compared to the no effect level for the most sensitive species.

[Slide.]
For triclosan, we may observe some transitory algistatic effects on some algal species under worst case conditions. I should note that there is other algae species where we had NOECs that are much higher, but these should occur only in aquatic environments close to the effluent pipe. It degrades quite rapidly in die-away studies, so we wouldn't expect significant downstream effects.

Also, triclosan is unlikely to have any

significant effect on non-algal species.

Thank you.

You are going to hear now from Elizabeth Scott via audio.

DR. WOOD: We are going to I understand have the slides on the screen.

The Case for Infection Control Practices in Home and Community Settings

DR. SCOTT: Good morning, everybody. This is Elizabeth Scott at the Simmons Center for Hygiene and Health in Home and Community Settings at Simmons College in Boston.

Thank you for allowing me to talk to you by phone today. I am busy here preparing to host a Conference on Cleaning for Healthy Indoor Environments for Children.

In the short time that is available, I want to provide some background information on the types of infection issues that can arise and describe a community-based approach to co-targeted hygiene that can be applied to these issues.

In the interests of time, I would like to

go directly to Slide 3 that is headed General Historical Perspective.

[Slide.]

The history of advice on cleaning and hygiene and infection control dates back at least to the mid 19th century and the age of the sanitary reformers, but today, there is a renewed interest based upon emerging infections, such as SARS and influenza, and other new viruses, a better understanding of the role of cross-contamination and person-to-person transmission of infections, concerns about antibiotic resistance, and the growing number of immuno-compromised groups in the community.

[Slide.]

This diagram illustrates the central position of the home in the community and the constant movement of microbes in and out of the home.

[Slide.]

In terms of infectious agents and infection control, the home is a multifunctional

setting which lends itself to the transmission of pathogens within the home.

[Slide.]

There are three main sources of pathogens into the home, namely, humans, pets, and food, especially raw meat and poultry, and fresh produce.

[Slide.]

In terms of food preparation and consumption, CDC estimates that there are 76 million Americans who get a foodborne illness each year, or 1 in 4 of the population.

Many studies have indicated that more than 50 percent of Salmonella and Campylobacter infection are actually home based, and not acquired outside of the home.

In the United States, 50 percent of raw chicken is contaminated with either Salmonella or Campylobacter, and this means that all poultry prepared at home must be considered to be contaminated and treated accordingly.

Contrary to popular opinion, even for organisms such as E. coli O157, it has been shown

that the majority of suspect hamburgers are prepared and eaten at home.

[Slide.]

Pets in the home. More than 50 percent of homes in the English-speaking world contain a cat or a dog, and cats and dogs and other pets can serve as reservoirs for a host of pathogens, which can be excreted into the home environment and can be picked up by hand contact.

[Slide.]

With regard to daycare in the United States, there are 13 million children under the age of 6 in daycare, and these children are at increased risk for upper respiratory infections and gastrointestinal infections at a much greater rate than children not in daycare.

They also are consuming antibiotics at a much greater rate than children not in daycare.

In daycare settings, the most common agent of diarrheal illness is rotavirus.

[Slide.]

At-risk communities at home. There are

many individuals at high risk for infection in the home, and, in fact, approximately 25 percent of the population in the USA is considered to be immunocompromised.

The majority of these are composed of elders over the age of 65 years of age, and today, there are 36 million or 12 percent of the population are over 65. This is estimated to grow to 20 percent of the population, or 71.5 million over 65 by 2030.

[Slide.]

Home based healthcare delivery in the USA. The USA seems to be leading the way in shifting healthcare into the home setting. Patients are either not admitted to hospital, but are treated as outpatients, and admitted patients are discharged into the home where they continue to be nursed.

Eight million patients are nursed at home in the USA, and 66 percent of these are over 65 years of age.

[Slide.]

Even outside of the home, there are many

situations in the community which lend themselves to a high risk of infection transmission especially those containing young children and elders.

Hand transmission of infectious agents can occur in all community settings. Handwashing facilities are not always available, and there is a general lack of awareness of the importance of handwashing in reducing the transmission of an infection.

[Slide.]

There are a number of examples in the literature of hygiene failures and outbreaks of infection, many of them involving hand transmission including infant salmonellosis, E. coli 0157, Staph aureus and MRSA, rotavirus and small round structured viruses.

[Slide.]

Shigella sonnei, dysentery, Group A streptococcal infections, Clostridium difficile, and infections for patients with cystic fibrosis especially Stenotrophomonas.

[Slide.]

Targeted hygiene. It is accepted that the risk assessment approach, similar to the HACCP approach that is used in the food industry, is best

applied to home hygiene, and it is necessary to devise a hygiene policy which has real health benefits.

This approach has come to be known as targeted hygiene. It involves hazard characterization, or in other words, identifying the sites and surfaces in the home where pathogens are most likely to be found, as well as considering whether the pathogens will be present in numbers which represent an infectious dose and the probability of human exposure to the hazard.

[Slide.]

Here we have an example of this kind of modeling. In this example, we are looking at three sites, namely, hands, food, and environmental surfaces, and the model considers the risk for infection at any one of these or group of these sites based on accumulated knowledge and then specifies the required approach to hygiene at the

site.

If we look at the row for hands, we see that the risk for infection transmission is considered to be constant and therefore, the hygiene requirement is frequent, targeted, and effective practices.

[Slide.]

The model discusses the use of the term "hygienic cleaning," and this term refers to the removal of dirt, as well as the reduction in the numbers of pathogens, either by removal or by killing them with a disinfection process.

The choice of a specific procedure including a hand hygiene procedure is situational dependent.

[Slide.]

It is important that hygiene standards are maintained throughout the community, that is a given, and that hygiene initiatives should be based on risk assessment and focus on reducing exposure to harmful numbers of pathogens.

It is considered that this targeted

hygiene approach is likely to be the most effective in preventing infection and, at the same time, the least likely to disturb exposure to harmless and even beneficial microbes.

[Slide.]

So, to begin to sum up, the home is a multifunctional setting with scenarios of increased risk.

An infectious disease continues to be a significant threat in these settings.

It is well documented that transmission of infection occurs throughout a range of community settings, including the home, and that throughout the community, hand hygiene is a primary defense against infectious disease.

It is clear that home and community hygiene practices offer benefits in terms of reducing the level of cross-contamination.

[Slide.]

Hygiene practice becomes even more important with the current concerns about antibiotic resistance, and it should not be

forgotten that hygiene promotion raises standards of hygiene awareness and practice, both in the home and in the general community.

Finally, it is recognized that effective home and community hygiene practice includes the targeted use of antimicrobial agents.

Thank you. This brings me to the end of this brief presentation.

DR. WOOD: Dr. Scott, are you going to be available later or should we address questions to you right now?

DR. SCOTT: I can't be available later.

DR. WOOD: Let's see if there are questions now.

Are there questions from the committee?

[No response.]

DR. WOOD: If she can stay on the line, let's leave it like that.

Let's move ahead.

Role of Hand Hygiene in Preventing Transmission of Infectious Diseases

DR. WEBER: Members of the Committee, and

guests, thank you for the opportunity to speak to you today about the role of hand hygiene in preventing transmission of infectious diseases.

I am a Professor of Medicine in Pediatrics at the School of Medicine, University of North Carolina, and Epidemiology at the School of Public Health. I serve as Medical Director of Hospital Epidemiology and Occupational Health at the UNC Healthcare System, and as epidemiologist of our General Clinical Research Center.

[Slide.]

The topics I want to cover for you today are: rationale for hand hygiene; the link between professional and consumer hand hygiene; indications for hand hygiene at home and community settings; efficacy of hand hygiene in reducing daycare center-associated infections, and uses of hand hygiene products in home health.

[Slide.]

Now, of course, I am only going to go through some examples. Many infectious agents are acquired either via hand contact with contaminated

surfaces, or this can occur through contact transmission and healthcare. Of particular importance are MRSA, VRE, and increasingly, C. difficile; in child care, MRSA, particularly community-associated, a growing problem; in the home, MRSA, cold viruses, herpes simplex.

Fecal-oral transmission occurs particularly in child care, Shigella, E. coli 0157:H7. In the home, many of the agents that we just heard about from Dr. Scott.

Hand hygiene is effective in reducing or eliminating transient flora. Hand hygiene is demonstrated to be effective in preventing illness, especially fecal-oral diarrheal illnesses, in healthcare facilities, child care centers and homes, and households.

[Slide.]

This is just a way, from one of Dr. Rutella's and our articles of looking at it. You have a colonized host or environmental reservoir. That person contaminates the inanimate surfaces, principally hands or the environmental surfaces.

They can lead to direct infection or they can contaminate other vehicles, such as food. You need an infectious dose and a susceptible host, and you can either get colonization or infection.

We can obviously break that cycle by surface disinfection or hand hygiene.

[Slide.]

Just one study again to show the efficacy in hospitals. This is the D. Pittet's study showing that as hand hygiene increased, both handwashing and alcohol-based products, the incidence of MRSA decreased in his hospital.

[Slide.]

Turning now to child care, we have already heard from Dr. Scott, the large number of children in child care. These include homes which are quite small, family daycare, which is slightly larger, and centers with many children, which has 4 million at least persons in it.

[Slide.]

Now, infants and toddlers require diapering or assistance in using a toilet,

obviously leading to contamination both of the hands often of the infant, as well as the daycare provider.

They explore the environment with their mouths, so contaminated toys or other potential areas, they will touch their mouths and become contaminated.

They have poor control over their secretions and excretions.

Immature immune systems.

Require lots of hands-on contact with healthcare providers.

Toddlers also have frequent contact with other toddlers leading to toddler-to-toddler transmission.

[Slide.]

Just some studies from the literature. Here, the baseline is the rates of disease that a child would have in their own home compared to a child care center, which are centers with many children, child care homes generally with 3 to 6 children, and you can see several studies showing a

higher risk of diarrheal diseases in child care homes, small group settings, compared to a single child, and certainly, all the studies show an increased risk in child care settings. The risk is usually between about 2- and 4-fold.

[Slide.]

Not surprising, a variety of syndromes and specific pathogens have been associated with child care centers, and this is only a partial list.

Of particular importance are the diarrheal diseases and hepatitis, hepatitis A, of course, fecal-oral transmitted, norovirus, rotavirus, E. coli 0157, Shigella, and Cryptosporidium. Many of these have in common being very low inoculum diseases easily transmitted person to person, and environmentally stable agents.

Respiratory syndromes have included otitis media, sinusitis, pharyngitis, and pneumonia, are particularly important besides viral. Respiratory pathogens are Haemophilus influenzae type B and Strep pneumoniae, although their importance has decreased with new conjugate vaccines.

[Slide.]

If one looks at the cost in millions, and this is old data, 15 years old, you can see the

large cost with most of it being absent from work for the homemakers, but, as well, just the treatment costs for respiratory infections, otitis, and long-term care running into the hundreds of millions of dollars. Again, this is 15-year-old data.

[Slide.]

Again, a simple way of looking at transmission within the daycare center environment. You have an index case that introduces the disease to the center. They will transmit disease to both personnel, they will contaminate fomites, they can directly contaminate children. Those fomites can contaminate the personnel and other children.

This is just a simplified way. Again we can break that cycle with both hand hygiene and with surface disinfection.

[Slide.]

Again, a variety of studies. Dr. Kotch

and I have collaborated. You can see two of our studies listed there. Dr. Kotch is Vice Chair of Maternal and Child Health at the School of Public Health.

These are very hard studies to do. We talked about that, it was mentioned by the panel earlier. First of all, the unit of analysis is the daycare center, not the individual child, because children's risks within the daycare center are not independent events, so you have to randomize daycare centers, as did all of these studies.

So, that is very difficult to deal with centers that don't generally don't want to do research, they worry they will get labeled as research, obtaining informed consent in this circumstance, and dealing with centers scattered over a very large number of areas.

Of course, funding is a problem, so very little etiologic work has been done. A variety of interventions have been used, most of which included hand hygiene and education. I should say education is critical and does have to be ongoing.

Our hospital turns over its personnel about 20 percent a year. Most of our daycare centers, because people are paid minimum wage and

have lower education, turnover of their staff 200 percent to 300 percent per year, so they are turning over their staff two to three times every year.

But you can see, particularly in diarrheal diseases, a variety of studies, all studies that randomized, had a control group and an intervention group showed a reduction of diarrhea. Our last study showed a 50 percent reduction of diarrheal days in the children. We also showed a reduction of diarrheal days in the daycare center providers.

[Slide.]

This is the more complicated scheme of how this works, again from one of our articles. Obviously, it is community prevalence is what leads to children becoming infected. Fecal-oral contamination of fomites and of hands, and of food secondarily.

Oftentimes, these centers use the same

food, the same surface for both diapering and food preparation, exposure to enteric pathogens, the agents have to survive, have adequate contact. Again, handwashing and surface disinfection can serve for decreasing these rates of illness.

[Slide.]

Indications for hand hygiene in the home. Much of Dr. Scott's targeted approach would be before and after preparing food, she mentioned greater than 75 million foodborne illnesses a year, before and after using the bathroom, before and after diapering for the reasons we just covered.

After pet and animal contact, I will remind you that there are more than 300 zoonotic diseases, many of which are contact to fecal transmitted, fecal-oral transmitted, and before and after providing healthcare. Again, that is increasingly being done in the home.

[Slide.]

We already talked about some of these studies. Dr. Larson's study, of course, did not show a difference, the study by Dr. Sandora did

show a 50 percent reduction in secondary diarrheal rates, again, the initial case coming into the home, and the secondary transmission are being decreased.

Again, these are very hard studies to do, and since your unit of analysis for many of these studies is the daycare center or the home, they have low power.

Other problems with the studies are the limited number of studies, the small sample size, many design obstacles working in this environment, lack of funding for these studies, multiple routes of exposure, exposures outside the home, and most of these studies don't use a true placebo group. Rather, there is a control group that uses soap and water.

[Slide.]

So, in conclusion, infections acquired in healthcare facilities and daycare centers result in substantial morbidity and cost.

Infections acquired in healthcare facilities and daycare centers often result from

person-to-person transmission via the hands of healthcare or daycare providers.

Hand hygiene may reduce the frequency of nosocomial and daycare center infections.

Hand hygiene likely provides a benefit with selected targeted activities in the home.

Thank you very much.

DR. WOOD: We will move on to the next speaker.

Importance of Fomites in the Transmission of Infectious Diseases

DR. GERBA: Thank you for the opportunity to speak to you today. My name is Chuck Gerba and I am a Professor of Environmental Microbiology at the University of Arizona, and I study how microorganisms are transmitted through the environment from one person to another.

What I want to talk to you about today is exposure. What we do is look at what is the exposure to microorganisms in various types of environment. That kind of information is useful to target interventions and to assess the success of

interventions.

I am also going to sum up the other presentations.

[Slide.]

I don't think many people often realize it, but 80 percent of the common pathogens in your hospital and home environments are actually spread through hand contact, particularly diarrhea and respiratory illnesses.

[Slide.]

This is important because about every three minutes, a child brings his hand to his face, nose, or mouth, and we touch a lot of objects in our normal working day. We have monitored people in offices, and you would be amazed how many different objects you are going to be touching during a normal working day.

So, there is a lot of intimacy with your environment even as an adult, I don't think many people realize.

[Slide.]

We have done studies on the occurrence of

fecal bacteria, E. coli, Klebsiella, Citrobacter on hands after different activities of adults and children, and actually, interestingly enough, preparing a meal is when you are going to get the greatest number of fecal bacteria on your hands, and the least, people exiting a toilet, so if you are going to kiss somebody's hand, make sure they didn't make a meal for you and came out of the toilet, I guess you could say.

[Slide.]

But there is a lot of things we don't realize. Children actually, when they go out playing, get a lot of fecal organisms on their hand, and doing the laundry is one of the higher risk areas, too, because you are handling the wet laundry and transferring it to the dryer, and wonder where all the brown streaks go, they go onto the laundry.

These are activities in which you get exposures you might not recognize, which might be good targets for interventions.

[Slide.]

Detection of pathogens on fomites has been done in numerous studies. I just wanted to point out hard surfaces, E. coli, influenza,

parainfluenza, norovirus, a cause of diarrhea, clothing, laundry, towels, Salmonella, hepatitis, norovirus, E. coli. Many of these will actually survive washing and drying to end up on your dried laundry.

In the bathroom, your sinks, taps, Giardia and Cryptosporidium are parasites that have been isolated, shigella, of course, norovirus.

Kitchen, our studies and others around the world have shown Salmonella, Campylobacter, E. coli in the kitchen area.

In schools, again, an array of microorganisms that cause diarrhea and respiratory infections.

[Slide.]

I just wanted to give you some numbers on some of these to give you an idea of what are some areas where you are going to be finding these microorganisms. We have looked at coliform

bacteria, which are again like E. coli, Klebsiella, where do you find them and in what kinds of numbers.

Of course, the greatest numbers occur in the kitchen area, not in the toilet area, which often surprise many people, but they like to grow in your sponges. In our study of 600 sponges around the United States, we found Salmonella in 10 percent. Actually, some of the people who think they are the cleanest, are dirty, when they wiped everything up, they spread the E. coli and Salmonella all over the kitchen.

So, people aren't aware of what these activities do a lot of the times. The cleanest area, if you want a refuge for enteric organisms, run to the toilet seat. It is really interesting, and that is why these studies are useful, because they are not always intuitive where you are going to find the microorganisms.

[Slide.]

Another way of looking at an exposure is to look at where most contaminated bodily fluids

are. This is urine, feces, saliva, mucus, blood. Daycare centers, largely because of the sanitary habits of children haven't been developed, of course, is a hot spot. Again, playgrounds, bus travel. I can't compare it to air travel, so I can't tell you.

But down on the end, fortunately, are physicians' offices, which I would like to congratulate you on that, you are keeping control of your bodily fluids.

[Slide.]

What about your office and work environments? This is the total number of germs, this is the total number of bacteria. Where might we want to look for, if we want to look for a pathogen in this type of an environment? In phones and desktops come out number one.

It turns out nobody ever cleans the desktop until they start sticking to it, because the janitor or crews won't touch it, it's personal space, so you would be amazed how many things you can find on a desktop over time.

Of course, the cleanest place in your office again is your toilet seat. There is something about toilet seats.

[Slide.]

What about your home and your daycare center, what about actual real pathogens? We have been looking at this. I show example of influenza virus. We looked at influenza virus in homes and daycare centers at different parts of the year, and you can actually see influenza beginning to appear on daycare center surfaces about late September or early October, before you usually see the first cases being documented clinically, and it continues to build up, peaking right before, the peak cases, usually in March or April oftentimes.

But, on average, these results are where you will find the flu viruses basically, almost about 40 to 50 percent of the surfaces during the peak of the flu season will have the flu virus.

We also went into homes where a child was ill for more than three days and looked at that environment, too. Again, you can see that with one

child ill with the flu, it really managed to make its way around the house.

Again, interestingly enough, the phone and the remote control, TV remote control, I guess which is obvious. You call the daycare center, the kid is not going to be there. You throw them in bed with the TV remote control, so those tend to get the most contaminated, I guess.

Another point being is that surfaces do get contaminated. People pick these up. On the righthand corner here is showing the flu viruses and cold viruses can survive up to three days on these surfaces and remain infectious.

[Slide.]

Fomite cleaning, I want to point out is not enough. We and others have recently done studies looking at cleaning. We studied an outbreak at a university in Arizona, and we were able to get in there right during the outbreak and found 18 percent of the surfaces in the dormitories were contaminated with noroviruses. They went in and cleaned the facility, and that increased to 48

percent. Basically, their cleaning spread them all around the facility.

The same thing in E. coli and public restrooms. We have been studying public restrooms, which are cleaned and not cleaned, and cleaned with disinfectants, and normal cleaning procedures with soap and water actually spread the organisms around the restroom.

So, I just use this to point out that cleaning sometimes isn't enough, particularly for the average consumer may not be aware that you also need to use a disinfectant in there and take other precautions when you are handling it, because you can end up actually spreading the organisms around.

[Slide.]

Conclusions from this. Hand contact plays a significant role in the transmission of common infections. Fomite contamination by pathogens is a common event in the home and work environments.

Washing fomites with soap and water is not enough really to prevent the spread of pathogens. You need more barriers than that in controlling the

spread of pathogens in these types of environment.

[Slide.]

Overall summary. I will try with the talks that were given this morning. Targeted hygiene, and I emphasize the word "targeted," is needed for home infection control. The benefit is prophylactic. Of course, you don't see the results necessarily are real to people right away.

Topical antiseptic wash products do not contribute to decreased antimicrobial susceptibility.

Extensive data indicate environmental risk from individual active ingredients are unlikely.

The data clearly support the current proposed labeling indication to decrease bacteria on the skin.

Finally, the 1994 TFM log reductions after a single wash, that is, about 2 logs, are appropriate as long as standardized ASTM methods are employed.

Thank you.

Committee Discussion

DR. WOOD: Thank you. We will have a couple of minutes for questions, and then we will break at 12:00 for lunch, because we have to be

back for the public comment period at 1:00. So, let's take questions for the presenters.

DR. PATTEN: We have heard that these biocides rapidly degrade. Could somebody tell me what they degrade to?

DR. REISS: [Inaudible reply.]

DR. HALDEN: Can I comment on this? It is actually quite interesting. I think we all have to realize that the data we see is largely driven by the way the studies are designed. That is true for all the data we have seen today, so we have to keep that in mind as we evaluate them.

There was a critical study that was done in 1975 by a person named Gledhill from the Soap and Detergent Association, and he studied the breakdown of triclocarban using carbon dioxide C14 evolution as a definitive tool of mineralization.

The study, if you read the abstract, says that triclocarban easily degrades to more than 90

percent and is readily biodegradable. If you read the article closely, you will see that the chemical was first put into raw sewage where it persisted for 10 weeks without seeing any change in concentration, and then it took an acclimation of an activated sludge for several weeks before degradation was apparently kicking in.

So, I completely agree with the industry that triclocarban is biodegradable. In fact, the microbiological dogma holds that there is not a single compound that cannot be degraded other than elements maybe, can only be reduced.

So, there is no doubt about it that this chemical can be degraded. The question really is what is happening in the real world right now, and I am still wondering why we use all these models and predict the concentrations if we can, if we have the methods in the lab, we just take a water sample wherever we feel it is important and analyze what is in the water.

Now, we have done our best with the limited means that we have to do that, and the

concentrations we find exceed by far the concentrations reported by the industry.

There is no point I think in extrapolating if you can actually make a definitive measurement, so the biodegradation there, it is critical to take a look at how these studies were designed and also to take a look at what happened at the plant. I showed you the data here. There is no controversy over the fact that milligrams per kilogram quantities of triclosan and triclocarban are present in sludge.

This is after we provided excellent opportunity for microorganisms, both aerobic and anaerobic microorganisms, to degrade these chemicals. This is an optimized process. We have spent hundreds of years to optimize it for biodegradation, yet, these chemicals come out of the process.

I think to claim that they are easily biodegradable is in part true, but in reality, it doesn't really matter. It counts what we see, it doesn't count what is possible.

DR. WOOD: I was lost by that, I must say. I would like the two of you to speak again about this. I heard two conflicting presentations. One

was that the material was found in sludge, and the other one was that it was degraded in sludge with a half-life of a few hours.

Four times a few hours means it should all be gone in that time, so these are incompatible positions, so we need to explain that.

Were yours measurements, or were they modeled?

DR. REISS: I didn't say that it wasn't present in sludge. It is present in sledge in ppm levels in the data that I have seen.

DR. WOOD: What was the half-life?

DR. REISS: The half-life in sludge?

DR. WOOD: Yes.

DR. REISS: Well, it's not easy to calculate a half-life from a wastewater treatment system, but a significant amount of the mass of triclosan that goes into the system is going to be biodegraded. Not all of it will be, some of it

will be present in the sludge, and the measurements we have are maybe 1 to 5 to 10 ppm for triclosan.

So, I think the next question after that is would that pose a risk, and that is something I am personally looking at right now in a lot of detail, but as far as the human exposure, it is inconceivable to me how you would see from a ppm level in sludge, anything near the exposure you would see from the normal use of these products.

It is my understanding they are present in like 1 percent in these soaps, and whatever, so from a sludge standpoint, I just don't think that that is a plausible high human exposure pathway.

DR. HALDEN: May I comment on this?

DR. WOOD: Sure, of course.

DR. HALDEN: I think, you know, we can't have it both ways. If we claim that these chemicals are effective, and we have produced data to support their use, then, they are effective, but once we are done with them, their effectiveness not miraculously disappears.

Now, we have ppm levels in sludge. In

sludge, we have all the microorganisms we are concerned about. If you would test for your pathogens, you would have orders of magnitude higher levels than you find in these homes, the data we just saw.

So, I think it is very important to consider that the pathogens are now exposed to very high levels of these chemicals in the sludge, in large quantities for long periods of time. It's happening, there is no doubt about it.

DR. WOOD: Other questions? Mary.

DR. TINETTI: I was sort of curious. I think we certainly got a nice presentation that I think we are convinced there is a lot of bacteria around and certainly where there are children, there is even more bacteria around.

Also, the presentation showing that hand hygiene in general is probably beneficial in decreasing those bacteria and perhaps infections, but what I didn't hear is any discussion of whether the products we are discussing today have any benefit at all over soap and water, and I was just

sort of curious why the complete lack of discussion of that important topic.

DR. WOOD: Does someone want to address that issue? I guess the FDA first. They looked at this.

DR. TINETTI: Well, I think the FDA addressed it, but this was for the industry people.

DR. FISCHLER: George Fischler from Dial Corporation.

I think that is essentially the crux of the issue of why we are here today. We are operating under a system of a proposed monograph that sets a level of efficacy for determination based on data that FDA has accumulated over the years, and is currently using in the NDA process approval for healthcare products used for this very purpose of infection control.

So, I think what our position is, is we are not essentially saying that every product that currently exists out there may provide a benefit. We represent manufacturers' efficacious products.

We are saying that we believe that

products, when they meet a standard as proposed by the FDA, not only meet the label indication as proposed in the monograph, which is the decreased bacteria on the skin, but being that consumer handwash products and healthcare handwash products are designed essentially to do the same thing, to reduce cross-contamination, and thereby to reduce the risk of infection.

The only difference is the setting in which they are operating, but really the risks are the same, and therefore, the efficacy levels are tied together.

DR. WOOD: I think what Dr. Tinetti is asking is are there data that you want to offer that show a difference between this and soap, handwashing with soap.

Was that the question, Mary?

DR. TINETTI: Yes.

DR. WEBER: This is Dave Weber. There are a couple of issues here, one, of course, soap and water are effective in removing microbes from the hand physically, and the settings in which other

products are particularly useful is when you don't have soap and water.

One of the problems we had in daycare, when we tried to do everything in the hospital in daycare, of course, they are in church basements, and if there isn't a bathroom or a sink in the room, you can't tell them to build one. So, in our last study, which we actually did show a reduction, we actually gave them physically, we put units in the intervention centers.

One was about the size of a refrigerator, one was the size of a stove, that had sink, separate handwashing, separate food services, stepcans, all the things that would help to correct some of the structural barriers. So, there are times that non-soap and water products are beneficial, because there is no option to use soap and water.

DR. WOOD: But we are talking about the home, not the daycare.

DR. WEBER: The second issue is that, or course, soap and water is effective, and just with

the drug that is very effective, say, 80 and 90 percent effective, to show that another product would be 5 or 10 percent more effective is a huge sample size, and, well, you can put hundreds or thousands of patients into drugs and vaccine trials, it is a lack of funding to do a trial that would truly be powered to look at the difference between a good product and a slightly better product or better product, and again we need to randomize homes or centers would be a truly monumental undertaking, conceptually easy, logistically and fundingwise very difficult to demonstrate that.

DR. FISCHLER: If I could just briefly respond I think to the basis of the question. In the documentation over the period of time that industry has submitted to the docket, and some of which was reviewed today, some of which is in, I think, the printed packet, but wasn't verbally reviewed, there is data showing differences between products containing--handwash products containing antimicrobial ingredients and matched placebos

showing that there is a significant difference in a standardized handwash test between the two products.

DR. WOOD: It's just after 12 o'clock, so let's break for lunch.

[Whereupon, at 12:05 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:05 p.m.]

Open Public Hearing

DR. WOOD: We are ready to begin the open public hearing, and I think the first speaker is on the phone, is that right?

DR. GOLDMAN: That is right.

DR. WOOD: The speakers have been given their times in advance, and we are going to ask you to stick to these times. Just to help to stick to the times, your microphone will be switched off at the end of the agreed time. First of all, I will read the instructions.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement to advise the committee of any known financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Goldman.

DR. GOLDMAN: [By telephone] -- Pediatrics for Harvard Medical School and Professor of Immunology and Infectious Diseases at the Harvard School of Public Health. I have more than 30 years of experience in infection control and hospital epidemiology, and have published numerous papers

relevant to infection control and hand hygiene.

Pfizer requested that I submit a letter and make a statement discussing the benefits of alcohol-based hand sanitizers. Although Pfizer compensated me for my time in preparing this statement and the supporting letter, the views and conclusions are entirely my own.

I am speaking in support of the wide use of alcohol-based hand sanitizers in healthcare institutions and community settings including the home. Alcohol-based hand sanitizers rapidly kill both bacteria and viruses that cause infections in these settings.

As is well known, they are effective against virtually all nosocomial pathogens of interest with the possible exception of spore-forming organisms, such as Clostridium difficile.

They also are extremely effective against the specific viral, respiratory, and gastrointestinal pathogens that cause the majority of community infections in pediatrics, as well as a

broad array of bacterial pathogens that are important in the community setting.

They are safe, convenient, portable, and better tolerated than repeated handwashing with soap and water.

First, I would like to address the use of these agents in healthcare institutions. They are the linchpin of efforts to curb transmission of infections in the hospital and are recommended by virtually all authorities and agencies for this purpose, and hygiene with alcohol-based sanitizers is central for the patient safety campaigns of WHO, CDC, and the Joint Commission.

Indeed, WHO's local patient safety challenge, just launched on October 13, heavily emphasized the importance of reliable use of alcohol-based hand sanitizers. Increasing use of these agents is a major focus of infection control programs worldwide.

Regarding use of viricidal and bactericidal hand hygiene agents in the home and other community settings, proof of principle was

established years ago by Owen Henley's group, which demonstrated that coating fingertips with iodine reduced the secondary attack rate of respiratory infections among mothers in the household.

My group recently published two peer-reviewed papers in the Journal of Pediatrics on the use of alcohol-based hand sanitizers and the rate of infectious diseases in the household. In the first study, a prospective observational study, we observed that the use of alcohol-based sanitizers was associated with reduced respiratory illness transmission in the home.

In a second study, a cluster randomized trial of multifactorial interventions emphasizing alcohol-based hand sanitizer use in the home, we demonstrated reduced transmission of gastrointestinal illness within families with children in daycare.

Although a statistically significant effect was not seen on the transmission of respiratory infections, the study suggested a better effect in families that used larger

quantities of hand sanitizer per week.

Both of these studies indicate that alcohol-based hand sanitizers may play an important role for the prevention of infectious diseases in communities. The validity of this claim is supported by at least two studies showing reduction in school absenteeism in classrooms where alcohol-based hand sanitizers were used.

Given my previous comments about the bactericidal and virucidal effects of alcohol-based sanitizers, these results are hardly surprising. The characteristics of alcohol-based products are especially advantageous in the home where busy family members have frequent exposure to infectious agents while caring for children with respiratory and GI disease, such as diaper changing, wiping snotty noses, and so forth.

The potential beneficial impact, both economic and social, of these agents is enormous. I strongly believe and recommend that the use of alcohol-based hand sanitizers should be encouraged in the home and community because of their

benefits, convenience, and minimal risks.

Finally, it seems arbitrary and counterintuitive for healthcare leaders and public health agencies to champion alcohol-based hand sanitizers as a primary intervention to reduce transmission of methicillin-resistant Staph aureus or MRSA, and other dangerous pathogens in the hospital while failing to support the use of these agents to protect family members in the home.

This is an especially important issue in an era of epidemic MRSA in the community and the threat of pandemic viral disease.

Thank you and I can stay on a few minutes if you have questions.

DR. WOOD: Let's go on to the next speaker, who is Sally Bloomfield from Pfizer. I think she is here and going to use PowerPoint.

DR. BLOOMFIELD: Thank you very much. I again have been asked to talk about the topic of alcohol-based hand sanitizers, and I have to tell you that Pfizer have supported me to prepare this presentation and to attend this

meeting, but the slides have been prepared by myself, and the conclusions and the opinions that I will give you are entirely my own.

The organization within which I work is called The International Scientific Forum on Home Hygiene, and I have to tell you Elizabeth Scott also is a member of the Scientific Advisory Board of this organization.

It was an organization which was established back in 1997 in response to the need for an independent organization which could develop and promote an understanding of good hygiene practice based on the emerging amount of scientific evidence which was becoming available to us.

One of our very earliest activities was to review this literature in detail, and to produce guidelines on home hygiene which are based on the targeted approach which Elizabeth talked about this morning. I am going to draw on this data for this presentation.

What Elizabeth showed you this morning, I hope, was that good hygiene practice is still key

to reducing infectious disease even in this 21st century where we have access to clean water, sanitation, and the necessary drugs.

She showed you, too, that good hygiene practice is important both in the home particularly, but also in those settings which form a continuum with the home - social, workplace, and travel settings.

In formulating an approach to home hygiene which deals with these risks, what the IFH has done is to adopt a risk assessment approach. This approach, which is known as HACCP in the food and pharmaceutical industries, is one that has been shown to be highly effective in controlling infectious transmission risks, and it has now become apparent that it is important to apply this approach both in the hospital and also in the home.

Applied to the home, it has come to be known as "targeted hygiene."

Targeted hygiene starts from the understanding that infectious disease agents are continually brought into the home, and Elizabeth

has already just demonstrated this. The main ones as far as hand hygiene are concerned are people, food, and pets. But, of course, what we know is that these organisms can also establish themselves in wet sites, such as basins, cloths, and so forth, and become a permanent source in those places, too.

The absolute key thing about targeted hygiene is that it is not about trying to eradicate pathogenic microbes from the home and community settings through daily intermittent cleaning.

It is about understanding where the pathogens come from, what are the sources, how are they transmitted, and intervening at the key places and at the key times to prevent the transmission and to avoid exposure by family members.

If you do the risk assessment, a semi-quantitative risk assessment, what you find is that targeted hygiene, because it focuses on preventing germs, the major target sites are hands, hand contact surfaces, such as door handles, and so on, food contact surfaces, cloths in the kitchen, bathroom, and toilets, but the indications are from

all the data that the hands are absolutely central, are absolutely key, the most important agents for disease transmission.

The data to support this comes from two sources. First of all, the Handwashing Intervention Studies, and I am not going to dwell on these, because Dr. Aiello and others have dealt with these very robustly this morning, but what I have done here is to take the eight studies from Dr. Aiello's review, which I think are relevant to developed country situations. They come from U.S., Canada, and Australia.

For all of these, which were carried out in community settings, and looked at the reduction of diarrheal and respiratory infections, in all of these, there was a significant reduction, which ranged from something of the order of 21 percent up to 77 percent.

The other data in support of the high importance of hand hygiene is the microbiological studies, the whole range of microbiological data which has been generated, much relating

specifically to home and community settings, which shows that infectious disease agents are continually brought into these settings, they disperse to hands and other surfaces, they survive for significant periods, and they can be transferred via the hands to the mouth, the nose, the eyes, and other surfaces in sufficient numbers to cause infections.

It is my firm belief that in view of the problems of performing clinical trials for prophylactic measures such as home hygiene, we must use these data in processes, such as quantitative microbial risk assessment, for assessing infectious risks and the impact of hygiene practices.

An equally important part of targeted hygiene is to understand that in situations where there is significant risk of infection transfer, then hygiene procedures are needed to reduce the risks by eliminating contamination as far as possible and preventing further spread.

For hand hygiene, in using soap and water, the key aspects of this is, first of all, that the

soap detaches the organisms, releases them from the skin, but very importantly, if soap and water washing is to be effective, it must be applied with a thorough rinsing process. It is that rinsing process which actually takes the organisms off the hands and makes them germ-free.

So, because we know that soap and water is not always available or freely available, especially in out-of-home settings, there is a key need for products that are portable, convenient, waterless, and effective.

"No rinse" alcohol-based hand sanitizers meet this need for maintaining hand hygiene when soap and water are not available and when homes are not visibly dirty.

Let me have a look at the data which supports this statement. If we are going to have a no-rinse hand sanitizer, what are we looking for? We are looking for three things. First of all, activity against a broad spectrum of bacteria, viruses, fungi representative of infectious agents commonly found in home and out-of-home settings for

which there is evidence of spread via the hands.

It must be fast acting and they must be equally or

preferably more effective than soap and water.

It is my belief that the available data

indicate good efficacy profile. This comes from

in-vivo tests, reduction of bacteria and viruses on

artificially contaminated hands; in vitro,

time-kill studies and intervention studies.

Let's look at them briefly.

First of all, in vivo testing, looking at

reduction of microbes on contaminated homes, there

is a large body of evidence out there, and I fully

recognize that the efficacy of different products depends on the formulation, it depends on the

strain of the organism, and it depends on the

method that is used.

What I am tried to do in this very brief

slide is to give a fair representation of the most important of those studies. So, against bacteria,

we can see that there is good activity, 2.6 to 3.7

log reduction against gram negatives and gram

positives, three test species, which is, for E.

coli, can be shown to be equivalent at least to that provided by soap and water washing.

Against viruses, there is an activity which ranges from 0.8 to greater than 3 logarithms, and for two of these organisms, the studies were done in direct comparison with soap and water and found to be equally effective.

There is a couple of key points to say here. One is, of course, that traditionally, we know that antimicrobial agents are less effective against non-envelope viruses, and you can see that for the most part, apart from hepatitis A, all of these are non-envelope viruses, but having said that, they are the ones which are representative of those which are commonly transmitted in home and community settings - rotovirus, adenovirus, rhinovirus, and norovirus.

The in vitro tests show that the activity extends to a broad range of organisms, for bacteria and fungi, giving good log reductions. The in vitro tests also show that the activity is equivalent to that against bacteria and viruses,

against envelope viruses, and importantly, you can see that that includes influenza A, which is obviously an organism of considerable concern at this present time with regards to threats posed by avian flu.

The non-envelope viruses, the in vitro tests do suggest lower activity, but activity of the order of 1.2 to 2.7 log reduction. Interesting, for example, for some strains of rhinovirus, that activity is much increased, a log reduction of 4.25.

Intervention studies, again, I am not going to describe them in detail, Dr. Aiello did that very ably, but all I have done here is to summarize the eight intervention studies which were carried out looking at the impact of alcohol-based sanitizers in home and community settings on gastrointestinal, upper respiratory tract infections, and absenteeism.

I again accept all the limitations which Dr. Aiello put forward, most particularly how do we separate the impact of health education, hygiene

education from the impact of the product, and the other being the lower activity against respiratory tract infections, but if you take them together, 11 out of these 15 studies suggest a significant reduction, which is of a similar order.

I know that you cannot compare the two, but they are of a similar order to those which were demonstrated in the handwashing interventions which we discussed earlier.

Turning finally to safety, it is my belief that the evidence suggests that alcohol-based hand sanitizers have a good safety profile. There is no evidence of alcohol or antibiotic resistance associated with their use. They have a non-selective action which precludes this problem of shared target sites of transmission of resistance elements on pathogens.

They evaporate to leave no active residue, and they retain activity against antibiotic resistant strains, such as MRSA.

EPA concludes that aliphatic alcohols are not intended for ingestion of low toxicity, and

thirdly, if they are formulated with the appropriate emollients, they cause less skin irritation than soap and water in frequent-use situations.

My conclusions therefore are: that home hygiene practice is key to reducing the burden of infectious disease in the community;

That hand hygiene is a key component of good hygiene practice;

That alcohol-based hand sanitizers provide an effective alternative in situations where soap and water are not available and may encourage compliance;

Finally, that based on their safety and lack of antimicrobial resistance/cross-resistance, they are appropriate for use in consumer settings.

What I am saying is that the benefit-risk profile is positive, and I believe that these products should continue to be recognized as safe and effective for use in consumer products.

DR. WOOD: Thank you.

The next speaker will be Lawton Seal.

DR. SEAL: I am a full-time employee of Healthpoint Limited. It is a branded pharmaceutical company, and today I wanted to talk

to you about antibacterial handwashes. These are alcohol-based formulations that have persistence added to them.

In general, consumer products for hand antisepsis do not routinely have formulations designed to provide either persistence or residual effects. Now, in the eyes of some, this allows for relative rapid regrowth of the flora and therefore perhaps requiring frequent product applications to maintain some degree of hand antisepsis.

Alcohol-based formulations can be produced that provide prolonged antimicrobial action, may be used with or without water, and do not overtly damage the skin.

Given the importance of this product indication to the general public and to industry, we elected to take a look at some of these in comparison to others.

Now, our testing was all done at a

third-party independent laboratory, none of it was done in-house. Supporting data was obtained employing two different test methods, one of them being the TFM test for healthcare personnel handwash, that being the Tinwash [ph] study that is done using Serratia marcescens as the indicator organism. This test is accomplished in a matter of a few hours.

In addition to that, there was a 5-day in vivo persistence assay, similar in concept and design to the surgical scrub test, allowing for 7-day washout baseline assessments as per the surgical scrub assay.

Now, there were four product applications applied daily within about the first hour of the arrival of the subjects, and these were applied per product instructions, various instructions, therefore, the application time specifically for the water-aided products did vary following applications and drying of the products, subject's glove, and then post-application samples were taken at 1 minute, 4 hours, and 8 hours on days 1, 3, and

5.

Now, both water-aided and waterless products were tested and these results were published.

Very quickly, to walk through this data, you can see that alcohol, that does have persistence factor in it, does give you indeed good kill at wash 1, and sustains that following the 10th wash. Compare that to 61 percent alcohol without a preservative, and one can see a difference that is statistically significant.

When this study is carried out to 5 days, you have an opportunity then to view perhaps a different situation, and that again the alcohol that is preserved continues to provide good kill over the entire course of the 5-day test at immediate time kill 4 hours and 8 hours, however, unpreserved alcohol is a bit spotty, particularly in its kill. I refer you to the publication as some of these differences are statistically significant.

Finally, we took a look at water-aided

products again using the TFM in vivo test. Note that at wash 1, again the preserved alcohol does well, as does 2 percent CHG, 0.5 percent triclosan. The latter two had a 30-second application, the preserved alcohol a 15-second application. Note, however, at wash 10, only the alcohol and the CHG-based products are able to clear the 3-log hurdle. That is in the final monograph of this product indication. Triclosan did not, if you will, make the cut.

When this is extended to a 5-day study, I think the differences between the product, specifically as it relates to triclosan, becomes even more obvious. One can see the 2 percent CHG and 61 percent alcohol, properly preserved, did well. For this particular study, we also added 4 percent CHG as a intra-study control as our test organization was quite familiar with this one.

To bring this to a rapid conclusion, these data support our assertion that antimicrobial persistence is available to the consumer. TFM-like testing in some format should be employed for these

consumer products.

This would provide adequate information about the level and duration of antimicrobial action. Perhaps they may serve best in some targeted indication that has been discussed in the course of this discourse today.

Thank you very much.

DR. WOOD: Thank you.
Charles Haas.

DR. HAAS: Thank you. My name is Chuck Haas. I am Betz Chair Professor of Environmental Engineering at Drexel University. I want to show you how to connect microbial reduction studies with risk assessment to estimate potential benefits when using antimicrobial hand products.

Some qualifications and a disclaimer. My work has been supported by CTFA and SDA, but I have been developing microbial risk assessment in a variety of contexts for over 20 years. I am a Fellow of American Academy of Microbiology, Society for Risk Analysis, as well as AAAS.

I will give you the conclusions upfront

and then restate them at the end.

Microbial risk assessment can be used to quantify the benefits of use of antimicrobial-containing consumer hand products.

For the particular scenario that I have presented here by way of example, the use of such products resulted in a reduction in median risk from a single exposure by a factor of 3 to a factor of 16 depending on the active ingredient.

The underlying methods are studies that were performed using the Health Care Personnel Hand Wash data that were conducted by various companies on different organisms. The log survival ratios were analyzed by myself and my student at Drexel to get statistical distributions, and then we performed Monte Carlo simulations with that data according to the procedures that we have outlined in a paper that is in press, in International Journal of Hygiene and Environmental Health, which I believe is part of the submission.

The data was collected by SDA and CTFA from their member companies, compiled by a

contractor from company records. All the studies were conducted by a single laboratory according to the ASTM method, and the summarized inactivation ratios, as well as the study conditions, were transmitted to us for analysis.

This is a 50,000-foot overview of the studies. Each study may have had anywhere from 4 to 15 or 20 individual data points, a number of different test organisms, a number of different active ingredients including 3 of the ones that I have heard under discussion today - alcohols, TCC, and triclosan.

The scenario that I have considered for this demonstration of a risk assessment methodology is one in which a person preparing a ground beef meal contacts ground beef that may contain E. coli with their hands.

The E. coli is transferred from the ground beef to the hands. There may be an intervention by either washing with plain soap and water or by decontaminating the hands with an antimicrobial product.

There is transference after decontamination of the E. coli from the hand to the mouth, and then we had dose-response relationships

for E. coli that have previously been published by us on results from human feeding trials.

This is the bottom line for the non-germicidal, as well as 3 active ingredients. We show a reduction in median risk of anywhere from a factor of 3 for triclosan to a factor of 16 for the alcohols with C-hex in the middle.

This is for a single-exposure risk, so the risk numbers are low, in the range of 10 -10 to 10-8, but if you annualize that, and if you look at other possible scenarios, then, this can contribute to the overall burden of risk by a particular population.

Bottom line conclusions. A factor of 3 to a factor of 16 reduction. The individual components associated with the pathway of the organism from the ground beef to the mouth to cause infection are all available, they are all published in the literature, and they can be combined in a

fairly standard way that we have been using in a QMRA approach for the past 20 some-odd years.

There are additional slides in the packet which amplify and provide numerical data on the details of the simulation for those of you who may be interested.

Thank you.

DR. WOOD: A 16-fold reduction in risk should give you a very small sample size to have to be able to do a study of benefit. Have you recalculated what sort of sample size you would need to show a clinical benefit with that kind of risk?

DR. HAAS: This is a 16-fold reduction in risk for that particular route of exposure.

DR. WOOD: I understand.

DR. HAAS: I am not an epidemiologist, but you have to consider this risk reduction along with a background of other risks that would lead to the same clinical outcome.

DR. WOOD: The next speaker is Tammy Lundstrom.

DR. LUNDSTROM: Good afternoon. I am Dr. Tammy Lundstrom. I am an attorney, and I am a practicing infectious disease clinician at the

Detroit Medical Center, Assistant Professor of Medicine in the Division of Infectious Disease at Wayne State University.

By way of disclosure, I am representing the Association for Professionals in Infection Control and Epidemiology, which is a large nonprofit organization comprised of infection control professionals and infectious disease physicians throughout the United States. My travel is being reimbursed by APIC, but I am receiving no other compensation for today.

I would like to limit my comments on behalf of APIC to the alcohol-based waterless hand hygiene agents where, as Dr. Levy noted earlier today, development of resistance has not been of a concern.

The APIC does not recommend that alcohol-based hand hygiene agents serve as a replacement for traditional methods of hand hygiene

with soap and water especially when hands are visibly soiled or potentially contaminated with blood or body fluids.

Healthcare workers and the public at large should be encouraged to use soap and water, but alcohol-based hand hygiene agents serve as a valuable supplement to traditional soap and water hand hygiene.

We recognize that there are often times when people's hands come into contact with surfaces that may be potentially contaminated with pathogenic bacteria and viruses, but they do not have access to soap and water either because of the physical environment or because of mobility issues especially in the elderly.

In these instances, portable products that can effectively cleanse contaminated body surfaces without the need for water greatly enhance infection control activities. APIC therefore encourages the NDAC to endorse the marketing and consumer utilization of alcohol-based antiseptic hand hygiene products.

Alcohol-based products have been shown in the healthcare setting to increase, in some cases very dramatically, compliance with hand hygiene

practices, and has been shown earlier that is the number one way to prevent healthcare-associated infection in the healthcare setting.

Alcohol-based hand hygiene agents are widely and routinely used in the healthcare setting as a supplement to traditional handwashing with soap and water. It is important to acknowledge, though, that in 2005, much healthcare is provided outside of the traditional hospital setting. Home IV therapy is now a $5 billion industry with over 20,000 provider agencies in the U.S.

Fifty-two percent of all hospital-based procedures are same-day surgeries, which accounted for about 2.8 million procedures in 1996. In this day and age, about 80 to 90 percent of cancer care is actually provided in the ambulatory setting.

These statistics highlight the need for effective and safe hand hygiene practices in order to continue to reduce healthcare-associated

infections to the irreducible minimum outside of the four walls of the hospital environment.

Noted benefits of good hand hygiene practices include reduction in transmission of, and infection with, etiologic agents of upper respiratory infections including influenza virus and foodborne disease, and potentially community-acquired MRSA.

The CDC and APIC, the Society for Healthcare Epidemiology of America, and others, promote the use of waterless alcohol-based hand hygiene agents as part of respiratory etiquette programs to attempt to reduce the spread of influenza, SARS, and other respiratory viruses in the ambulatory and community setting.

The merits of alcohol-based hand sanitizers in certain situations have also been noted by other governmental and accreditation agencies, such as the Centers for Medicare and Medicaid Services and the Joint Commission.

The message that good hand hygiene practices, including the use of waterless

alcohol-based hand hygiene agents can reduce the potential for spread of bacteria and viruses, and this is becoming increasingly recognized by consumers of healthcare services.

In closing, I feel it is important to reiterate APIC's position that alcohol-based products play an important role in the overall infection control and prevention including community settings, such as those described above.

Therefore, on behalf of APIC, I would encourage the NDAC to endorse further development and use of alcohol-based antiseptic hand hygiene products in the appropriate clinical circumstances.

Thank you.

DR. WOOD: Thank you.

The next speaker is Harold Bochnek.

MR. BOCHNEK: Good afternoon. My name is Howard Bochnek, and I am the Director of Technology and Regulatory Affairs for Veridien Corporation.

We hold patents for and are distributors of a family of hard surface disinfectant products that are registered with the EPA, and antiseptic

hand wash and hand wipe products that are marketed under FDA's enforcement policy for OTC drugs that are not the subject of a final monograph.

Our hand antiseptics contain 70 percent isopropanol by weight and are represented on our labels as containing 75 percent isopropyl alcohol by volume. Our hand antiseptics have successfully been used in medical and dental offices, hospitals, and other clinical and nonclinical settings for the past 10 years.

I am here today to advocate for the continued use of isopropyl-based antiseptics and antiseptic handwash products for both professional use and for use by the general public.

While I recognize that the thrust of today's meeting is more geared towards the general population, it is our position that whatever position that the FDA takes with regard to what populations should be using on a routine basis antiseptic handwash products, if you decide to include the public in that, which we would endorse all the other speakers have spoken on behalf of

that position, we believe that isopropyl alcohol-based products should be included in that final monograph, as well as for healthcare professionals.

The literature is filled with studies supporting a variety of chemical formulations as hand antiseptics. As you know, in October of 2002, the Centers for Disease Control and Prevention published a report that cited nearly 400 peer-reviewed published studies.

In particular, in their Guidelines for Hand Hygiene in Healthcare Settings, the CDC cited numerous studies demonstrating the efficacy of isopropyl alcohol as an antiseptic handwash including a reference to the adoption of isopropanol in Europe as the standard against which all other antiseptic agents are measured, the equating of ethanol and isopropanol, evidence of 60 percent isopropanol solution being more effective than either Povidone Iodine or a 4 percent CHG solution, the superiority of isopropanol as an antiseptic agent compared to Povidone Iodine, 4

percent CHG or triclosan, and a similar finding in relation to ethanol, Povidone Iodine, or CHG. In my prepared remarks, which I asked to be distributed, which you should have, I have included the citations to all the published papers to back all that up.

Part of the CDC report contains recommendations for healthcare professionals. The first recommendation is to wash hands with soap and water when hands are visibly dirty or contaminated. The second recommendation states that if hands are not visibly soiled, use an alcohol-based hand rub for routinely decontaminating hands.

I also cite you to the first part of the CDC report wherein they set out definitions. In the definition section, they define that alcohol-based hand rub as a preparation containing 60 to 95 percent ethanol or isopropanol. This clearly represents the view of an expert governmental agency that isopropyl alcohol is a safe and effective active ingredient when used in an antiseptic handwash.

I am also sure that you are aware, as was referred to by the first public speaker, Dr. Goldman, that one week ago today, on October 13th,

the World Health Organization issued an advance draft of the WHO Guidelines on Hand Hygiene in Health Care.

That report echoes the conclusions of the CDC report, including each of the references made by the CDC and including all the findings as found on the CDC report, particularly with regard to those speaking to the efficacy of isopropyl alcohol as an antiseptic handwash.

I strongly urge that this committee support the conclusions of the CDC and the World Health Organization by also recognizing the efficacy of isopropanol and by classifying isopropyl alcohol as a Category I active ingredient for OTC antiseptic handwash or healthcare personnel handwash drug products.

Like the CDC and the WHO, I ask that your determination be based on the myriad of definitive published studies in the literature from both the

United States and Europe.

I thank you for the opportunity to appear today.

DR. WOOD: Thank you.

The next speaker is Dr. Cole, and he will be the last speaker.

DR. COLE: I am Gene Cole. I am a Professor in the Department of Health Science at Brigham Young University, and I will be presenting to you today the results of a recently completed, multi-year study looking at antibiotic versus antibacterial resistance and cross-resistance of skin bacteria from bodywash products, these products being liquid bodywashes, shower gels, antibacterial soaps.

This study has been funded by the Soap and Detergent Association, therefore, my time and involvement in the study design, conduct, analyses, interpretation, and so forth, has been compensated by SDA.

There were two independent applied research organizations that collaborated and

cooperated to effect this study, both located in North Carolina. Two target groups of organisms, Staph aureus and then coagulase-negative Staph species.

Sampling was done on the forearms of the subjects. We basically had three groups of participants, those that routinely, frequently washed, but did not use any antibacterial wash products, and then those who washed frequently and used antibacterial wash products containing triclocarban, and a third group, wash products containing triclosan.

Just to put some summary results upfront, these results further discount the speculative claim that the use of antibacterial wash products contribute to the selection and propagation of drug-resistant bacteria on human skin.

Out of a pool of several hundred qualified participants, we randomly selected them and broke them down into the three groups, as I previously described, those that regularly used triclosan-based products, those using triclocarban

products, and those who were dedicated to using no antibacterial wash products, but still washed frequently.

We had very stringent exclusion criteria. Participants could not have been on antibiotic therapy within the last 90 days, not have used any skin medications, medicated shampoos, anti-acne products, could not be employed in healthcare, daycare, animal care, could not be frequent swimmers or hot tub users, or routinely be exposed to solvents, all of these which, of course, can alter temporarily or permanently, to some extent, normal skin bacterial flora.

Our project team visited homes and qualified the participants based on an examination of their products and survey questions. The sampling was done as you see here. This was a composite sample with both arms using a sterile culturette swab, 64 square centimeters on each arm.

Forearm skin was used because it is less subject to transient organisms that might be picked up from the hands, wash less frequently. Again the

focus here was bodywash products.

The testing was done by a third-party independent laboratory using the microscan method, and the antibacterial susceptibility in terms of MIC values for the active agents was done by a standardized broth microdilution method in the published literature.

The panel of antibiotics are the 10 that you see here. Those highlighted in green are ones that we designate as preferred treatment drugs or first line choice of drugs.

Out of the study there were a total of 317 Staph isolates. Only 16 were Staph aureus, 301 coagulase-negative staph, and you can see the distribution of those amongst the three groups.

In terms of results, first and foremost, no isolates showed full or intermediate resistance to vancomycin. Then, moving on to methicillin resistance, there were only 2 of the 16 Staph aureus isolates that were resistant, giving a rate of 12.5 percent as compared to some notable citations in the public literature.

Fridkin et al. came up with a rate of 20.2 percent hospital and community-acquired staph isolates, this from a study involving 23 hospitals

in the U.S., the 50 percent rate from Europe where over 50,000 staph isolates from across Europe were accumulated.

Methicillin resistance with CNS, again, our rate was 20.6 percent compared to a combination of community-acquired and hospital-acquired isolates. The 73.3 percent were from cumulative data from 2000 to 2004 from Duke University Medical Center.

Here are the distributions and no statistical significance amongst the groups. Of course, the Staph aureus, too few numbers to even attempt that.

In terms of antibiotic resistance, in summary, all 10 drugs no significant differences among the groups for Staph aureus even when we pooled the antibacterial data, both the TCC and the TCS groups. Similarly with the 6 preferred treatment drugs.

Very similar with CNS. Distribution across all 10 drugs, no significant differences, nothing statistically significant even when antibacterial data were pooled. There was one that fell out that was significant. Greater tetracycline resistance in non-user group isolates.

When we looked at antibiotic resistance to more than 1 preferred drug, that is, 2 or more of the 6, for 69 isolates of CNS, you can see the rates of resistance there and across the 3 groups, nothing statistically significant, and, of course, the 2 Staph aureus isolates, too few in number.

In terms of antibacterial resistance, all 317 isolates were tested both against TCC and TCS, and again, across all 3 groups for CNS, there were comparable MIC values, likewise for Staph aureus.

Just to give you a sense of what we are dealing with here, these are ranges of MIC values against the 2 actives. If we look certainly at the upper MIC levels, they are consistent with TCC and TCS amongst all 3 groups.

For Staph aureus, again, all very

comparable, nothing stands out as being different and therefore statistically significant.

Cross-resistance testing. We did it two ways. First, as you see here, a good example. Coag-negative Staph, we took the 9 isolates that were most antibiotic resistant, that is, resistant to 4 to 5 of the 6 preferred treatment drugs.

These MICs for triclocarban were comparable across all 3 groups with none showing the highest MICs, however, there were higher MICs in less antibiotic-resistant isolates.

Similarly, for TCS, we found the same results.

Then, actually, working back the other way, there were 7 isolates that had the highest antibacterial MICs. First, for triclocarban that you see here. Looking at their antibiotic resistance profiles, the greatest resistance was to 2 preferred drugs compared to resistance up to 5 drugs shown by less triclocarban-resistant isolates.

For triclosan, there were 60 CNS isolates

that had the highest MIC values. We took those, we looked at their antibiotic resistance profiles and again across the 3 groups, there was no significant increase in resistance compared with less TCS-resistant isolates.

Staph aureus, again very few in number, but comparable values similarly.

To sum things up, these study results confirm similar findings from recent assessments of antibiotic and antibacterial resistance in home environments. The reference there is a study that I also directed and was published two years ago in the Journal of Applied Microbiology, and, of course, the recent paper just published by Dr. Aiello.

Again, to summarize our study results, and we will be writing this up and submitting this for publication, further discount the claim that the use of antibacterial wash products do contribute to the selection of propagation of drug-resistant bacteria on human skin.

Thank you very much.

DR. WOOD: Thank you very much. That was the last scheduled public speaker.

So, let's turn now to the question and

answer period for the committee and leading eventually to dealing with the questions which have been circulated.

Questions? Mary.

Question and Answer Period

DR. TINETTI: I just have a couple of points of clarification for the last speaker.

Number one, when one uses these bodywashes, is the forearm a common place that you would have much contact with these agents, and number two, what power?

We keep hearing one of the reasons why we can't do these studies is because the rate is so low that we would have large numbers, and I am just wondering what kind of difference you would have been able to detect with only 70 in each of the groups.

DR. COLE: To answer your first question, these are individuals that bathed frequently, at

least one or more times a day, and again we felt it was imperative to select an area of skin on the body that uniformly would be washed and would be less susceptible to transient bacteria from shaking hands, touching doorknobs, and that sort of thing.

The question of is 70 in each group strong enough power, as you know, all studies are limited by time and resources, and taking those two factors into consideration, these were acceptable powers, if you will, that we considered would be appropriate for the study.

It is interesting, too, as we began to analyze and write these results up, that again going back into the literature to see what studies of a similar nature have been done relative to human skin bacteria, change over time due to washing, and there is very little out there, nothing much at all.

This should be a significant contribution to the whole field of skin bacterial flora, as well as effects of frequent washing and use of antibacterial products.

DR. TINETTI: I am a little confused, and maybe you can correct me on this, is that you didn't use hands because you wanted to avoid the

transient contact that one would get with doorknobs, et cetera, but isn't that why we use the handwashes, to get rid of the bacteria that occur in exactly these kind of situations? I am confused about your methodology.

DR. COLE: Well, remember this wasn't a handwash study. The products were bodywashes, so therein lies the overall objective. Yes, their hands are going to be washed with these products, as well, but what effect does it have long term on skin flora that are not contaminated or in any other way altered by transient flora that might be picked up.

DR. WOOD: Did the industry representative want to say something?

DR. FISCHLER: I think Gene answered it at the end. The answer was that that was the stable community, and the question has come up of what happens to the stable community.

DR. WOOD: Dr. Halden.

DR. HALDEN: Just a quick question. The triclocarban-resistant strains or the minimum inhibitory concentration that you measured, can you tell us about the range of those for triclocarban specifically?

DR. COLE: About the antibacterial?

DR. HALDEN: Yes, the MIC range, you said there were some higher ones, lower. Can you tell us what the MIC was for the microorganisms?

DR. COLE: Well, I gave you the ranges there. You have them on the slides. Those are the complete ranges for each of the participant groups for all of the isolates from those groups.

DR. WOOD: Do you want to put that slide back up whoever is controlling the slides?

What are the units here?

DR. COLE: These are the ranges of MIC values.

DR. WOOD: So, these are concentrations, right?

DR. COLE: Yes, those are the

concentrations.

DR. WOOD: In what units?

DR. COLE: Micrograms. It's the standard micrograms per liter. We started off with a concentration that was based on the standard stock solutions, as well as a serial dilution scheme that would ensure that we had an endpoint.

DR. HALDEN: So, if this is micrograms per liter, there would be 23 parts per trillion, 23 nanograms per liter?

DR. COLE: That would be right for triclocarban.

DR. HALDEN: It's a very low number.
DR. WOOD: How does that compare with what you see, which is obviously the question you are raising?

DR. HALDEN: Well, I think that these values are very, very low, and I am concerned about the values that we find. The values you find in the environment are much higher, and I need to get a feel for what the MIC is. Per milliliter? Okay. Thank you.

DR. PARKER: I had a question. There were a couple of references to the alcohol-based hand sanitizers being better tolerated than soap and

water. I would like to just hear a little bit more about what that means exactly.

DR. WOOD: Who wants to take that? I guess somebody from the Pfizer group.

DR. OETTE: Dagmar Oette from Pfizer.

There are published studies in the healthcare setting that looked both at effectiveness in terms of antimicrobial reduction on the hands and tolerance in terms of looking at skin dryness and cracking, and I think in some studies, actually doing measurements of water loss, that in comparison to soap and water, that the effectiveness of the alcohol-based products that have emollients are still antibacterial, and that in terms of water loss from the skin or changes in skin texture, that they are actually less than what you see with soap and water, which can dry the hands even more because they don't always contain emollients, the bland soaps.

Also, I can tell you that just from the products that we have in conjunction with Gojo, that we do standard cumulative irritation studies of the finished product to look at skin tolerance, and haven't observed any major problems with that.

DR. WOOD: But my recollection was that

these studies compared multiple repeated handwashes, which is not what is being proposed in the consumer environment.

DR. OETTE: I think the current consumer was actually recommended for repeated uses.

DR. WOOD: No, but the ones that compared the tolerability of the repeated handwashing with water and soap in the hospital setting was multiple times in the one day.

DR. OETTE: Correct, and I think a consumer who went out of the home would use a product like this multiple times in one day, and the studies--maybe I could ask--

DR. WOOD: Wait a minute. There is data that shows that people like you and me, who wash our hands with soap and water three or four times a

day, do better in terms of tolerability with alcohol wipes?

DR. LI: We have a study we submitted to AAD--

DR. WOOD: I am sorry, could you introduce yourself.

DR. LI: I am Qing Li from Pfizer Consumer Health.

We have a study, we submitted a poster to American Academy of Dermatology meeting last year compared to a different concentration of alcohol washing in the consumer setting, washing the hands at least 10 times a day for 14 days, compared the skin irritation both by the investigator and by a consumer to see if there is any change at baseline versus 14 days later. There is no significant change at baseline versus 14 days later.

DR. WOOD: So, the question I think that Dr. Parker was putting to you was that there was a claim to be better tolerability for these products than handwashing with soap and water. What is the basis for that, she is asking.

DR. LI: That is the studies published in healthcare setting.

DR. WOOD: So, your studies that you just

described that were submitted last year don't support that in the home setting, is that right?

DR. LI: Compared to the soaps directly.
DR. WOOD: I see. Okay.

Other questions? Do you want to move on?

I am sorry, Dr. Levy. Go ahead.

DR. LEVY: I would just like to take Dr. Cole to task here, because he says a long-term study. To me, 30 days is not very long. Two, I don't remember whether the groups were randomized or not randomized, they were asked how many times they used soap.

Finally, I am not sure that any one study discounts what you call a speculation that is based on science in the laboratory and our vast experience with antibiotics. This is the second time you said that.

So, you tell me what 30 days represents.
DR. COLE: This wasn't a study where

individuals used the products for just 30 days. This was not a prospective study, we did not give these participants in these home environments the products to use.

As we surveyed these individuals, and we confirmed the products that they used in the home environment, we found that most--and I haven't calculated the percentage--but close to 100 percent have used these products routinely for years and years and years.

In fact, some individuals have used a particular product, such as Dial soap, for example, because their parents used it, and they have always used it. Again, we are looking at residence microbial communities on skin, free from transient organisms, trying to look at is there a significant relationship between the regular, routine use-- we are talking years here for the majority of these participants, not just 30 days--is there any indication that it is leading to increased antibiotic resistance.

I can say something similar back to you,

and that is, we have just a few laboratory studies indicating that there is a relationship between certain antibacterial agents and targeted mechanisms of activity. I am not going to dispute that, but this is just one more study that is showing that what we have right now in the home environment, the use of these products, we don't see the threat or the risk that you, yourself, sometimes expound upon.

DR. LEVY: Well, let me put it this way. I hardly ever say that a single study discounts. You have said it twice. I mean it is only a study. We have shown, and other labs, that, yes, it does occur in the laboratory. We have also shown that out in the environment, there are bacteria in the staphylococci, among the enterobacteriaceae, which have increasing levels of resistance to triclosan, and we are now looking at some of the other.

What I am saying is something is going on, but a single study, such as yours, which is, as you now say is relatively sort of single site look-at, we have done similar studies. We need to be able

to design the right studies if we are going to be able to fully put the questions out for the answer.

But, you know, to think that one particular study makes that kind of a difference is stating it I think a lot stronger than any of us do.

DR. COLE: Well, as I pointed out, this is the third study, one of which is yours.

DR. LEVY: Yes, but you saw how we concluded our study, right? That more studies should be seen because what we looked at was--you have a certain limited amount and a limited amount of time. We looked at a year. You looked at I guess we don't know how many years, because you looked at people that had been using it for a certain amount of time, right?

DR. COLE: Right, and again most in years.

DR. WOOD: On the limited amount of time, let's move on.

Are there any other questions from the committee?

DR. TINETTI: I guess I would like to pose

this question to see if anybody from industry can address it.

I guess I would sort of summarize what we have heard today. There is clearly benefit to hand hygiene, nobody can doubt that, that soap and water is quite effective, it is not always available. That alcohol-based wash sanitizer is a good alternative when soap and water is not available.

We have also heard that the triclosan, although it may be as effective as soap and water and/or alcohol may not have some adverse consequences both to the individual and to the environment.

I guess I just want to ask the industry, given I think which is a reasonable, not overstatement of the evidence that we heard today, what, if any, role there is in triclosan. I am still trying to figure out where the non-alcohol-based sanitizers, what role they might have given the lack of evidence of any added benefit and potentially, some evidence of harm, sort of what their sort of take-home message would

be to us today.

DR. WOOD: Does somebody want to take that question from industry? I think the question that is on the table, just so we make sure we get the answer, is that no one is arguing about the benefits of washing your hands with soap and water, and what is the evidence of clinical benefit from washing your hands with something other than soap and water.

DR. TINETTI: Well, it is not clinical benefit, because there probably is clinical benefit, but the question is with potential harm and other products that are clearly beneficial, what unique role might it have.

DR. WOOD: Right, okay.

DR. FISCHLER: I guess I would dispute the harm statement firstoff. I think, as we have heard today, it is a very controversial issue, and as with any scientific argument, there are positions on both sides, and scientists will be the last one to tell you that this is the last word on anything.

So, I guess my position is that, you know,

I am convinced that I do not see the risk from it.

But I guess again it comes down to if your question

is what role do antibacterial soaps other than, let's say, alcohol can play given the fact that

plain soap and water in many situations provides a

level of benefit, what is the role for these other

types of soaps, is that essentially your question?

DR. TINETTI: What unique role does it have? Granted that there may not be any harm, but

good scientists can also say the lack, you know, no

lack of--

DR. FISCHLER: Correct.

DR. TINETTI: Well, my standard might be a little higher. I want to see that it is safe

rather than your wanting to see that it is not

safe. So, given what we presently know today, can

you inform us what added benefit--

DR. FISCHLER: I think I would position it as that there is no single product that provides an

overall benefit. We have heard the benefits of

alcohol products particularly in cases where soap

and water is not available, and also we have heard

that when hands are visibly soiled, that is a part of the CDC recommendation also, because of the nature of the effectiveness of alcohol, that you have to pre-wash or pre-clean your hands.

So, I think an effective antibacterial soap--and again I am going to stress--an effective antibacterial soap that meets the requirements as set down by the FDA in the monograph fills the gap of providing both the cleaning and disinfection piece, that alcohol provides only the disinfection piece. Again, I want to stress efficacious products.

DR. WOOD: I am still lost, I guess. So, we don't--run it for me again. We don't have evidence that it produces greater reduction in bacteria.

DR. FISCHLER: I would say that within the packet that the group has received--

DR. WOOD: In comparison to soap--

DR. FISCHLER: Yes, in comparison to soap and water.

DR. WOOD: So, in comparison to soap and

water, for the handwashes now, not the alcohol--

DR. FISCHLER: Right, correct.

DR. WOOD: So, your scenario is if you have got contamination of your hands, you should wash them--well, gee, that is a revelation I guess--

DR. FISCHLER: To some people, it might be.

DR. WOOD: Well, maybe. In addition to that, though, having washed them with soap and water, you get some incremental benefit from washing with an antibacterial soap. Now, tell us about that.

DR. FISCHLER: Essentially, antibacterial hand soaps are designed for the removal of transient bacteria. Maybe I will take a minute to sort of--when Dr. Rogers was giving her part, and she put up the industry position, talked about persistence and long lasting, it was actually reversed from what our position is.

We feel they should be broad spectrum, fast acting, and not persistent for handwashes,

because the role of an antibacterial handwash is to significantly remove the number of transient organisms on your hand that may play a role in transmitting disease or in cross-contamination.

So, given that there is a certain percentage of organisms that are removed by plain soap and water, whether it is in a home setting or in the hospital setting, there is that intuitive idea--and this is what we spent a lot of time on in March--an additional log reduction should provide a benefit. The question then was exactly how do you measure it and what is that log reduction.

We are working under the framework of the monograph. I won't spend any time on the surrogate testing, but surrogate endpoint testing proposed by FDA in the monograph sets certain efficacy log reduction levels for antibacterial products, and we are proposing that consumer products meet those same efficacy levels which are higher than for plain soap and water for consumer products, as well as for hospital products, because the risks--I think what we tried to convey today is that the

risks, whether they are in a hospital or in a home, are present. It is really just the setting that is different, and under targeted conditions, cross-contamination does occur whether it is a caregiver, a professional caregiver in a hospital or a nonprofessional caregiver at home.

So, again, what we are talking about are products that meet FDA's standard of efficacy, providing an additional log reduction above that which can be achieved with plain soap and water.

DR. WOOD: Dr. Clyburn.

DR. CLYBURN: I just was going to emphasize and just get you to comment. I know we are going over and over on this, but is there any justifiable, even potential risk unless you can show a demonstrable benefit for these products over soap and water?

DR. FISCHLER: I think the demonstrable benefit, if we go back to the standards that FDA has set, this is for both consumer and for healthcare products, the log reduction has set in the monograph assumes a certain level of benefit in

the high-risk situation or in a risk situation.

What we are saying is for that same risk situation, and we feel at least from the evidence that we have seen for risk being primarily development of resistance, which we do not believe is present in the studies, and I certainly will be the last to say that there should be no more studies on it, that this is the end of the story. I am sure this is far from the end of the story.

I think that given the lack of apparent risk from use of these products, and the associated benefit linked to the log reduction benefit, as FDA has found it over the past 30 years in determining what a log reduction or what derives to be a benefit, that there is a benefit in the home especially in this era when healthcare is more and more, or risk situations take place more and more outside of the home.

I think you could look at the same thing with alcohol. Alcohol, other than certain other attributes that it has, such as the fact that it evaporates, you don't have to clean your hands, you

don't need water, provides essentially the same level of efficacy, can provide the same level of efficacy, AB hand soaps can provide the same level of efficacy as alcohol when properly formulated.

So, that is all we are saying is that properly formulated products, whether they are alcohol, non-alcohol, non-alcoholic hand sanitizers, whatever you have, hand soaps, as long as they meet the standard of efficacy as proposed by FDA, and meet the safety requirements, should be allowed to be available to consumers as set up by the monograph way back in 1972.

DR. WOOD: Wayne, I am going to take you next, but I think Dr. Powers want to respond to that.

DR. POWERS: Since I have heard the words "FDA standards of efficacy" about 10 times in that sentence there, as you know, most of it, I just want to get it on the record for this advisory committee.

As we addressed back in March, we had some significant questions about this issue with

surrogate endpoints of decreasing bacteria on the skin. When we related that to a healthcare setting, we had very little information to relate that to clinical benefit.

One of the reasons why we addressed it again here was because here we actually had some studies which leaves some uncertainty as to the clinical benefit, which even more makes the surrogate in this setting rather questionable.

So, the other issue is that--and I also want to reiterate--clearly, when we are talking about systemic drugs, and it would apply here, as well, there are vast differences in the efficacy of products depending upon the setting in which they are used.

Therefore, the risk in a healthcare setting would seem to be much greater in terms of transmission of organisms and the susceptible hosts in that setting. Therefore, applying what occurs in a healthcare setting to the consumer setting is one of the reasons why we have separated these into different categorizations.

The last comment I wanted to make is the issue of it is impossible to prove safety. All we can do is rule out some level of risk. What we

have here is we are not even sure how to rule out levels of risk for antimicrobial resistance, because we are talking about we don't know how to measure it, what to measure, when to measure it, and when it might occur.

So, I think the regulatory standard actually is you have to prove your product is effective, and if you can't do that, it inherently tilts things towards the harm side regardless of whether one can absolutely prove that there is harm or not.

So, I just wanted to clarify those few points.

DR. WOOD: I think before we bog down too much in this, the first question that the FDA had posed to the committee actually addresses most of this discussion directly, so we will return to that in a minute or two.

Wayne, you have been very patient.

DR. SNODGRASS: My question relates to ages and young infants as an example. If we just take the soap and water versus alcohol based, and set aside the other antimicrobials for a moment, what would be from anyone's perspective, either labeling or how would you say what is the lower

limit of age for use, in other words, should a 1-month-old get an alcohol-based product?

The outer two layers of skin we know are thinner, we know there is greater skin absorption for a number of compounds, how would you address this, up to what age in years or months, or are there any thoughts on this?

Are they going to tolerate it, yes, and I will just put as an aside I am aware of cases, uncommon as it is, of 70 percent of rubbing isopropyl alcohol, as an example, if a little is good, more must be better, and a very young infant, and they are hot and somebody puts that on them at home, and enough to where they can produce coma.

DR. WOOD: That question may be rhetorical unless someone wants to take it.

In the meantime, let's move on to Terry.

DR. BLASCHKE: I have almost a little different kind of a question, and actually, it is for Mark Hartman.

What fraction, when we talk about the risks of the triclosan and triclocarban comes from the actual handwash products versus the stuff we use to wipe off the counters, and so forth? I mean is that found in those preparations, and is that a

larger source in the environment, that comes to the environment?

MR. HARTMAN: From what I was able to gather in preparation for this meeting, in terms of triclosan specifically, we estimate that the antimicrobial uses that are described, material preservatives and disinfecting, hard surface disinfectants or sanitizers would represent about 5 percent or less of the total use of triclosan in the U.S.

Does that answer your question?

DR. BLASCHKE: So, that means the other 95 percent comes from the handwash and bodywash

products, is that what you are saying?

MR. HARTMAN: I wouldn't be in a position to answer that, but I know that that would be a major source, in toothpaste, and so on, wherever else it is produced and used.

DR. WOOD: Anyone else? Any other questions? Sonia.

DR. PATTEN: I am wondering if there are other governments, other governmental agencies, other bodies of scientists in the world who have taken a look at the benefit-to-risk ratio and made the decision that it is too risky to incorporate these biocides in hygienic products.
I don't know if anyone can answer that. Is it banned anywhere for use in these kinds of products?

DR. ROGERS: I have looked for information from other countries, and I haven't found a lot, but I have found some information that some countries are having a voluntary ban on products containing triclosan. I am not sure if Dr. Halden has any more information on the European countries

or not about whether they have any bans on these products.

DR. HALDEN: Yes, I think in general the European Union is a little more concerned about environmental concentrations of certain chemicals, and so it has been recognized in the European Union that concentrations of triclosans are detectable in various media.

I know in Denmark and I believe in Sweden, there are initiatives to remove these chemicals from the market.

I believe that they have been removed from supermarkets in Great Britain, at least I have read some reports on triclosan-containing formulation.

There is a risk assessment document available issued by the U.S. of the Denmark Environmental Protection Agency that is downloadable from the Internet. Peculiarly, it is based a lot on the data generated in the U.S. because Denmark hasn't done a lot of studies.

So, you will see that they operate on the same data that we look at here, and they apparently

come to the conclusion that there are certain risks associated with it.

Since I am on here right now, I have three more questions or comments maybe regarding the presentations from the industry. First, I think we already talked about the concentrations of triclosan and triclocarban in biosolids, and I think it was clear now, if you don't have this information, I can provide it to you, the EPA also has detected triclosan in milligram per kilogram concentrations in municipal biosolids, and there is at least two other studies that I can give you.

Secondly, it was mentioned that the chemicals degrade, biodegrade. I think we talked about biosolids, and it was agreed upon that there isn't much degradation.

Then, it was mentioned that the triclosan is being degraded in the river very quickly and has a half-life of only a few hours. This is not biodegradation. This is a process of photodegradation. Triclosan has a hydroxl group that makes is susceptible to photodegradation.

If you have soil, if you have triclosan bound to a particle, it is not susceptible to degradation, photodegradation. Biodegradation is

actually very, very slow.

Also, I would like to put on the record here that there is a paper published in the early 1990s, reporting for two New Jersey wastewater treatment plants effluent concentrations of 6,000 parts per trillion, so 6 parts per billion of triclocarban in treated effluent. This is not a sewage spill, this is a normally operating plant that was in the early 1990s.

This information is available for you if you go and do a PubMed search. However, it didn't enter the EPA robust summary issued by the industry to the U.S. EPA for the risk assessment that is currently ongoing for triclocarban. So, it is an interesting piece of information that should be figured in.

I don't believe that there is any need for us to speculate what environmental concentrations are. Let's just use the data that are out there

and do the measurements that are needed. Thank you.

DR. WOOD: Did you want to respond to something?

MR. HOFMANN: Yes, I just wanted to respond on the question whether there is any ban in the world. I am Matthias Hofmann from Ciba, and being the marketing manager, I can assure you that there is no authority out there in the world known to me who has banned triclosan in the world.

DR. WOOD: I think somebody said that there was a voluntary--

MR. HOFMANN: There are some organizations, let's say, wanting to, like trade organizations or so, trying to restrict the use of triclosan in their shops, but there is no authority out there in the world.

DR. WOOD: Somebody said, I think the quote was that supermarkets in the UK were not selling it or something. Is that true?

MR. HOFMANN: That can be the supermarket chains, but that is not authority itself.

DR. WOOD: Charley.

DR. GANLEY: Can he just stay there for a minute?

DR. WOOD: Yes.

DR. GANLEY: I have something from the Internet here, and this is from October 26, 2000, and it says four Danish Government agencies have taken the unusual step of issuing a joint statement advising consumers against the routine use of antibacterial household and personal hygiene products. The agencies argue that antibacterials are unnecessary for domestic use plus potentially harmful to the environment.

Also, from February 16th, 2001, 6 Finnish public authorities today urged consumers not to use certain antibacterial chemicals. Organic antibacterials are not needed in households, and their growing use carries a long-term risk of spreading antibiotic resistance in microbial populations.

That contradicts what you just said.

MR. HOFMANN: No, I just said authorities

have not banned the substance.

DR. GANLEY: You implied that there were no voluntary requests by government agencies to not use these products.

MR. HOFMANN: No, they are not banned in a way that legislation is made to ban it.

DR. WOOD: So, government agencies have suggested in other countries that it not be used is what Charley is saying. Okay.

Any other comments, questions?

DR. REISS: Regarding biodegradation in sludge, we have a study by Federal that was published in 2002, which a radiolabeled study found that total removal of triclosan ranged from 98 to 99 percent in a laboratory scale activated sludge system.

DR. WOOD: I couldn't get that when you said that. How can he measure it then if 98 percent of it goes?

DR. REISS: You can still, it is still at a measurable level.

DR. WOOD: But his mass balance doesn't

work then.

DR. REISS: Well, his data are unpublished at this point. I mean I am looking forward to seeing it when it is out in the literature, and we will take a look at it, but we have this study that is published now, and it shows a 98 to 99 percent removal.

DR. HALDEN: Let me comment on this. This is an excellent work done by Federal. These are laboratory studies that look at carbon dioxide evolution, so there is a C14 labeled triclocarban, and you can really track it pretty much by the molecule what happens to the chemical.

These are all excellent studies including the one that was published in 1975 by Gledhill. My point is not that these studies are not any good. My point is that these studies observe a phenomenon that was seen in the laboratory.

You know, in the circus, we can make a bear ride a tricycle. You are very hard-pressed to find that bear ride a tricycle in the environment. So, I am more concerned as an environmental health

scientist to see what actually happens in the environment.

We are not the only group that finds that these microbials accumulate in sludge. This is a fact, and you have also the industry has produced a lot of data. They never bothered to do a mass balance because the mass balance truly reveals how little really is being degraded.

So, I don't argue with the outcome of these studies. These are excellent studies, but I don't think they address the issue that we are dealing with here today, that is, the environmental fate of these chemicals.

DR. REISS: First of all, just a small correction. Federal study is triclosan, not triclocarban. I think you said triclocarban.

DR. HALDEN: Sorry, I am addicted to the chemical.

DR. REISS: I thought you said that there is no biodegradation of the sludge. I may have misheard you, but this study I think clearly shows that that is occurring at a significant rate.

DR. WOOD: Unless there is something pressing, let's take a 10-minute break and be back here at 2:35, and then unless there are further

questions, we will start working our way through the questions.

[Break.]

Committee Discussion

DR. WOOD: Before we turn to the questions, are there any further general issues the committee want to raise or discuss, and before we move on to the specifics of the questions?

Hearing none, then, let's move on to the first question. I will read it to you.

As drug products, should consumer antiseptics be expected--I actually changed that "be demanded," because it was unclear to me what that "expected" meant there--be demanded to provide or expected to provide clinical benefit by reducing infection risk?

Charley, do you want to say anything about that, or, Susan, do you want to say anything?

DR. JOHNSON: Is there any particular part

that is unclear? I think the change to demand is consistent with what we intended.

DR. WOOD: Right, I would change it to demand because I was unclear as to whether that was asking whether we saw that effect or whether we should expect that effect in the future.

Any discussion on that? Yes, Terry.

DR. BLASCHKE: I might ask the question about whether or not--I am concerned about what I think is maybe too clear a distinction between the healthcare provider setting and the consumer setting, and I think there is some validity in this continuum model that the industry has talked about in the briefing document.

I wonder whether when we talk about clinical evidence, whether we would demand clinical evidence because it would be again an over-the-counter product that would be demonstrated overall in an entire random population of the public, or whether we would be interested in seeing data that came from perhaps what would be considered a higher risk population.

We have heard how much of the healthcare that is being provided these days is actually, in fact, being provided out of hospital. I think we

are all familiar with that, and I think it is reasonable to believe that there are subsets of the consumer population out of hospital, out of nursing care settings, and so forth, that, in fact, are higher risk.

DR. WOOD: That is really Question 2, which specifically addresses that.

DR. BLASCHKE: All right. Then, that is my comment.

Robert.

DR. TAYLOR: Actually, I had a similar question, and I guess what is our standard for these over-the-counter products, similar over-the-counter products, and I am a little concerned that if we apply the same stringency of proof that we do to prescription drugs, it is a little over the top, I guess. So, I would err on the side of a more liberal interpretation of this thing.

DR. WOOD: So, if it was something other than this, you would be happy if it hadn't shown any efficacy for a drug to go over the counter?

DR. TAYLOR: It has to show some efficacy in terms of in studies that have been demonstrated here, but what do you mean by clinical benefit, I

mean how do you define, do you mean in the most rigid way or--

DR. WOOD: I defer to Susan or Charley.

DR. JOHNSON: It might be helpful to the committee to go back to the healthcare antiseptics, which are OTC products. In the discussion of that population, there was an assumption about risk in that population, and there was an assumption that the product did need to show using one endpoint or another, and the discussion evolved into using the bacterial log reduction simulations as the correct endpoint, but the intent was to show that we had enough data to assume that the antiseptic products would have an impact on the clinical outcome, that they would actually reduce infection risk.

The question here is should consumer

antiseptics be expected to--we are not asking about the actual standard, that is a later question, but what should consumer antiseptics be expected to do in order to demonstrate that they have an effect as drugs, is reduction of infection risk the right--you can almost think of it as it is not an indication for the back of the bottle, but it is the action that it is intended to have, is that what a consumer antiseptic should be intended to do.

DR. TAYLOR: Versus removal of bacteria.

DR. JOHNSON: Versus any other endpoint.

DR. WOOD: Versus making you smell sweet first.

DR. TAYLOR: Or a placebo effect.

DR. WOOD: That's not a placebo effect, I know.

Ruth.

DR. PARKER: Can I just build on that to ask you, so is it the benefit of reducing infection, or reducing infection risk?

DR. JOHNSON: The historical evolution of

the antiseptics has been based on the premise that an antiseptic helps to kill bacteria, and that, in turn, is intended--you wouldn't kill bacteria if you weren't intending to decrease infection risk, and we are asking you whether or not that linkage is in place in your minds for consumer antiseptics or, in fact, is another benefit an appropriate benefit for the antiseptics.

Aside from what it might be, does the thought process that an antiseptic should be expected to reduce bacteria, which is intended to decrease infection risk, the right model for a consumer antiseptic?

DR. POWERS: Can I clarify the difference between risk and endpoints in trials, because I think that is what you are getting at. When we look at things like cholesterol, having high cholesterol is not a disease in and of itself. It doesn't make you feel bad.

By decreasing your cholesterol with a lipid-lowering agent, you decrease the risk of going on to get cardiovascular events and death.

The endpoint in those trials is cardiovascular events and death.

So, decreasing the risk factor has to translate into that actual event, namely, infection rates.

Does that answer the difference?

DR. TINETTI: So, can we change that to reducing infections as opposed to reducing infection risk, which I think would make that point clearer?

DR. WOOD: So, you are saying the question should read: As drug products, should consumer antiseptics be demanded to provide clinical reduction in infection? All right, got it.

Any other discussion on that? Jack.

DR. FINCHAM: I guess that I am struggling to make a distinction between something that may or may not be a prescription product, or may or may not be a consumer product relative to safety and efficacy. I think one of the real benefits to society that FDA provides is some assurance that what is on the market is safe and effective.

So, to me, to make the distinction that perhaps some wash can be FDA light approved or a different designation just makes no sense to me,

and I think it is disingenuous to the general public that assumes that we have somebody that can help us determine whether something is safe and effective, and whether or not something is approved as a prescription and over-the-counter product in my mind relates to how it is initially applied for. It doesn't necessarily deal with how effective or safe or anything else it is.

DR. WOOD: There is no suggestion I don't think, Susan, that there is a different standard for OTC efficacy from Rx efficacy, right?

DR. JOHNSON: The healthcare antiseptics are not prescription products, they are OTC products, so there is not necessarily a difference between those in terms of their OTC status.

The other thing that I just want to clarify about this question, subsequent questions are largely based on data that have been shown about infection rates and endpoints regarding

infection rates, and benefit-risk ratios, assuming that the benefit is somewhat related to infection.

So, part of the presence of this question is related to do you even support that model is a fundamental question here.

DR. WOOD: Wayne.

DR. SNODGRASS: Another way I am trying to get through this question and read it and interpret it is are we talking about a surrogate endpoint or a direct endpoint, which I think has been alluded to. We are not, okay.

In other words, there is no background, and I don't think there is any large set of background data that says we have so much data about an endpoint that we can now say there is a surrogate log order or whatever and use that instead.

DR. GANLEY: That is down to Question 3. It is really, if there is a use for these products, what is their use, what do they intend to use, regardless of what criteria, you know, whether you accept a surrogate or whether you require clinical

studies that show reduction in infection rate, what should be the expectation for these products, is it that they just decrease bacteria on the skin and do nothing else, or--it really gets a little, I don't want to get too complicated here--but most drugs we have give you specific directions of how to use them, what population to use them in, and what the expectation of benefit is going to be.

I think we are trying to apply that standard here, is that this is an antiseptic product, is the purpose to decrease the infections or risk for infection, however you want to characterize it, or is there something else that we are not seeing.

Even by the surrogate model that had been proposed back in 1994, and prior to that, it is really a surrogate saying that this is going to somehow lead to decreased infection rates.

John alluded to that earlier on, well, since 1994, we now have some clinical studies that say, well, these products may be no better than just washing your hands with soap and water.

So, what is the intent of the drug in this product then?

DR. WOOD: It seems pretty clear to me

that the question that is on the table here, which is what John was getting at, is there evidence that these drugs reduce infection. I mean that is the question, and, in fact, that is not quite the question.

The question now says should we expect evidence to be forthcoming that these drugs reduce infection before they get labeled as infection-reducing drugs. That's the nub of the question, right? Okay.

Any other discussion?

DR. FINCHAM: Just one more thing. I think that all of us are struggling to make an informed decision based upon the data and the science that is presented, and I don't know if Dr. Gerba is still here, but it was the last presentation before we broke for lunch, and he went through a series of numerous slides without any references, without any substantiation of where the

data came from, and I guess I get really concerned when figures are thrown out that 80 percent of pathogens in the hospital and home environment are spread through hand contact.

I guess I would just encourage the industry or other presenters to make sure that what they do present is documented, referenced, and available for us to try to make the best decision that we can on the data provided.

DR. WOOD: Well, of course, it is sort of post-hoc, isn't it? I mean just because it is spread through hand and through touching does not prove that an antiseptic handwash would reduce that, and that is the nub of the question, I think.

DR. FINCHAM: I don't want to go through each one of these, slide by slide, but I could.

DR. WOOD: Any further discussion?

If not, does everybody understand the question?

DR. FINCHAM: Is it rate or risk, did you finally decide?

DR. WOOD: It's rate, it's not risk. Risk

was deleted. So, it's by reduction in infection.

Risk was deleted.

So, if you are voting yes here, you are saying you demand that there is a proof of

reduction in infection.

We will start with Dr. Halden.

DR. HALDEN: Given the label of these

chemicals, I would expect that they have to show a reduction in infection, so my vote is yes.

DR. WOOD: Sonia.

DR. PATTEN: I vote yes.

DR. WOOD: Robert.

DR. TAYLOR: I vote yes.
DR. CLYBURN: Yes.

DR. PARKER: Yes.

DR. TINETTI: Yes.

DR. SNODGRASS: Yes.

DR. FINCHAM: Yes.
DR. BLASCHKE: Yes.

DR. WOOD: Yes.

DR. ARDUINO: Yes.

DR. OMEL: Yes, they should.

DR. WOOD: So, unanimously yes for that.
The next question is: Based on the

information in the background materials and today's

presentations, are there any populations--which gets to Terry's point--outside of the healthcare setting in which consumer antiseptic use has been demonstrated to be more effective than the use of plain old soap and water in reducing infection rates?

I guess we should deal with that first, because obviously, you know, they are greedy, and if you say yes to that, they are going to want you to enumerate which ones it is you see that, so be careful.

Discussion on that? Are there specific populations in which you have seen data that demonstrate these drugs to be more effective than plain soap and water?

Terry, do you want to go there or not?

DR. BLASCHKE: I think that we heard very nicely the limitations of a lot of the studies that have been done in different populations, whether it

is in a less developed population, underdeveloped population, healthcare, i.e., community care setting, schools, and so forth.

So, I think, looking at those studies, recognizing the limitations, there is certainly to me a pretty reasonable suggestion that, for example, in settings, as has already been discussed, where access to soap and water may be difficult, that, for example, the alcohol-based handwashes probably do have some added value.

DR. WOOD: Wait a minute. That is not what we are being asked.

DR. BLASCHKE: Further down, huh?

DR. WOOD: So, this is a straight comparison with soap and water here. I mean I think that is a different question which we will get to.

So, the question is are there populations in which the benefit has been demonstrated, demonstrated, not conjecture, Terry.

DR. BLASCHKE: Well, again, given the fact that most of the studies, as we heard, have various

limitations and confounding, I think none of those have probably been definitive.

DR. WOOD: Any other questions?

DR. TINETTI: Actually, as I sort of see, there is two pieces to this question. Number 1, is the sort of healthcare continuum model, is that well supported, and, if so, in those different populations, is there something better than soap and water.

I kind of challenge that first part of it is to sort of assume that--I mean there is no question that sicker people are out in the community than there used to be, but they really didn't provide us any real evidence.

The population I am most familiar with is the elderly, and sort of to make the assumption that 25 percent of people are immunocompromised because of the aging of the population just doesn't hold true. The vast majority of older people out in the community are quite healthy.

Those that aren't healthy who are in the community rather than in nursing homes don't

necessarily have the same cohort effect, and all of the other things that are spreading infections that occurs in the hospital.

So, to begin with, I am going to start with that part of the question, is that I take issue with the idea that, at least among the elderly population, that there is a large reservoir of people in individual homes that are going to be spreading infections in the same way it happens in healthcare environments.

DR. WOOD: Any other comments?

Let's take the vote and we will start at this side and this time with Dr. Omel.

DR. OMEL: I thought the information on alcohol-based hand sanitizers seemed impressive, so in the population that uses that product, I think that there has been some demonstration of effectiveness, certainly over soap and water.

DR. WOOD: The question is--let's read the question again. Has it been demonstrated to be more effective than use of plain soap in reducing infection rates. That's the question.

DR. OMEL: And that would include hand sanitizers?

DR. WOOD: I suppose, yes, I don't see why

not. So, has it been shown to be more effective than use of plain soap in reducing infection rates?

MR. OMEL: So, are hand sanitizers more effective than soap and water?

DR. OSBORNE: Excuse me, Mr. Chairman--excuse me, Doctor--it asks if there are any populations outside of the healthcare setting for which consumer antiseptic use has been demonstrated to be more effective. It doesn't ask which product or type of product has been demonstrated to be more effective.

So, aren't we referring to a population, such as what we looked at in the studies, a daycare center, a school classroom, isn't that what we are referring to rather than a particular type of product?

DR. WOOD: I think what Jim was saying, which obviously, he may want to stick with, is that the people who are using alcohol wipes might be a

population. I mean defined as, I don't know, but if you want me to do it, defined as people who couldn't get to soap and water, I suppose might be a population.

DR. OMEL: That is what I meant.

DR. WOOD: Okay.

DR. OMEL: In that regard, I would say yes.

DR. SNODGRASS: I would like to suggest that how you word this question is going to change your answer very markedly. If you want to separate it out by products as part of populations, I think that is going to make the question more clear.

DR. WOOD: Why don't we do this. Why don't we stick to populations defined as we normally would clinically, and then take people who have no access to soap and water and do them separately, because that is a product of--is that fair, Susan?

DR. JOHNSON: I think the intent of this question is to identify the level of data that we have seen, and have we established that in any

population, the use of any product is better than plain soap and water, and we will talk about subpopulations in the next part of this, but do we have any data that shows that these products work better than plain soap and water.

DR. WOOD: Okay. So, that's it.

DR. TINETTI: So, can we assume for this question that people have equal access to everything?

DR. WOOD: Yes, they have to have soap and water to be able to do it, so, given two bowls of different soaps.

Dr. Omel, does that help?

DR. OMEL: I still would feel that an alcohol-based sanitizer would be more effective than soap and water. I still vote yes.

DR. WOOD: All right, so you vote yes. I am not sure I understand the question, but go ahead.

DR. ARDUINO: If we are actually looking at populations--

DR. WOOD: Right, we are looking at

populations.

DR. ARDUINO: Then, I would really have to say we don't have the data, or the data is insufficient that we do have. So, the answer I would have to say is no.

DR. WOOD: I would say no.

DR. BLASCHKE: For the reason I said before, that the studies aren't definitive, because it doesn't--they are often confounded by the training, and so forth, so I would still have to vote no in terms of the definitiveness of the studies.

DR. FINCHAM: I vote no.
DR. SNODGRASS: No.

DR. TINETTI: No.

DR. PARKER: No.

DR. CLYBURN: No.

DR. TAYLOR: No.
DR. PATTEN: No, but I will qualify that. In Dr. Aiello's report, we did hear of a couple of community studies where there did seem to be an impact particularly on diarrheal diseases, but that

seems to be very preliminary data.

DR. HALDEN: My answer is no, too, but water has to be available. It's a different situation if there is no water, as we outlined here.

DR. WOOD: Okay. The second part of this question is: If yes, to which it was no, please describe the population and the category of consumer antiseptic that provided benefit, for example, antiseptic handwash, antiseptic bodywash, and hand sanitizer.

My sense is that the committee probably would want to address the antiseptic handwash there. If that fair, Dr. Omel?

DR. OMEL: My vote was basically, based on the hand sanitizers using alcohol.

DR. WOOD: The hand sanitizers comes in here.

DR. OMEL: The question comes down to three choices: antiseptic handwash, antiseptic bodywash, and hand sanitizers.

DR. WOOD: So, you don't want to address

that here?

DR. OMEL: Well, I still feel that the alcohol-based hand sanitizers have more effectiveness in the populations that would use them, more than just soap and water.

DR. WOOD: That is why I was giving you the chance to say that.

Anyone else want to add to that? We don't actually have to vote on that, I don't think.

DR. SNODGRASS: I would like to make a comment.

In the second part of this, where it says, "If no," and it gets into define a consumer population, it seems to me that, I am taking this, the way that is worded, strictly worded, I would interpret that to mean, well, I am going to have to find a significantly immune-suppressed population, of which there are some perhaps out there, in order to define that kind of a population. Otherwise, there would not be any of the population I could think of.

DR. WOOD: Let's deal with this first one

first, if yes. So, the only person who voted yes was Jim here.

DR. OMEL: I represent an immunocompromised person. I have been through a stem cell transplant. If I have to take care of my wife, who is bowel and bladder incontinent, when I prepare our food, if I have a choice between soap and water versus alcohol, I would prefer to use alcohol. If I am the population that represents immunocompromised people, then, I would suggest that we certainly would gain benefit by an alcohol-based wash product.

DR. WOOD: Any other comments on 2(a)? Now, let's go to 2(b). If no, what criteria should be used to define a consumer population for which washing with plain soap and water, or other hygiene measures that do not involve antiseptic drug products, are inadequate to reduce infection risk?

DR. TAYLOR: He just answered the question. It would be a population in which there was increased risk of infection because of

comorbidity.

DR. WOOD: Wayne?

DR. SNODGRASS: I really have very little to add further to add. I think the way I am reading this part of it is simply that for plain soap and water to be inadequate, then, that is as high-risk population. So, whatever defines that, it would be just that.

DR. WOOD: I think it could be more broad than just immune-suppressed people, though - individuals with diarrheal illnesses, individuals with upper respiratory tract illnesses, an enriched population that was already at risk and demonstrating that there was a failure of household transfer of the infection would be a pretty compelling study.

Remember, we are defining studies here.

DR. SNODGRASS: Right, but I would think that most of the age-related patients I see diarrhea, that soap and water is going to have a big benefit.

DR. WOOD: Right.

DR. SNODGRASS: A large benefit.

DR. WOOD: As I understand this question, they are asking here, asks to define the kind of

consumer population in which studies will be done to demonstrate a benefit.

So, I would see it as looking at enriched populations of people who are at particular risk, either their particular risk, or their caregivers, or their family members, or their post-contacts are at particular risk, in which it would be relatively easy to show a benefit.

Mary.

DR. TINETTI: I guess I am confused, because we didn't get any evidence today on any special populations, so is this question saying are there populations in whom these studies should be done, or are we asking the question, are there data out there to support that there are populations in whom these are more effective than soap and water. So, we need to clarify that question.

DR. WOOD: I read the question should--

DR. TINETTI: We should reword the

question.

DR. WOOD: -- what criteria should be used to define a consumer population for which washing with plain soap and water--so I was reading that as defining a population in which a study would be done.

DR. TINETTI: So, we are not supporting that there is any evidence right now, even in immunocompromised?

DR. WOOD: Right.

DR. JOHNSON: You said no, and this is the "no" part of the question.

DR. TINETTI: I am just trying to clarify are we saying that we should study populations, or are we saying that there are groups in whom we already should recommend.

DR. JOHNSON: Right. You are starting to recognize the problems we had in writing these questions, because we are trying to tease out some of the nuances here.

The first part of this question was, is there data presented, do we know that there is

data, and having said no to that, our question is, now, in what populations would define the consumer population, what sorts of criteria would you use, are they are immune-suppressed, are they the sorts of populations that were presented by industry where there is a lot of bacteria, daycare populations, what populations would you expect--

DR. WOOD: No, Susan, I think the question Mary is asking is are you asking us to define the populations in which studies should be done, or are you asking us to define populations in which we think there is a titillation of data.

DR. TINETTI: But I think Susan is saying if we answered no to this question, then, we already think there isn't data. So, maybe if we just add a little point there about in whom studies should be done.

DR. GANLEY: Or I think the other thing is it may also be a population that doesn't have access to water, so we are trying to define what criteria there is already a suggestion that someone who is immune-compromised and has to take care of

someone else who may be ill, that is defining a population.

Someone in a hurricane who does not have a house is a population, and have no access to water.

DR. TINETTI: But I think those are two different situations, because when there is no water, I think there is already compelling evidence that exists.

DR. GANLEY: But you need to define that, that is population that you are interested in also.

DR. WOOD: You mean you want us to define a population in a hurricane?

DR. GANLEY: No, but it's a population who does not have access to potable water, so they could not use soap and water, so what do you do to reduce the risk for infection.

DR. POWERS: One way to think about this is put yourself in our position. What we are supposed to do in terms of labeling for products is to apply appropriate conditions of use that tells the user how and in whom to use those.

So, if you think about it from that point

of view, it's trying to outline what would you like to see in labeling that tells you where and when to use these things if it was proven to be effective in a study

DR. WOOD: But what Mary is struggling with, I think, and I don't want to speak for Mary, but she is not clear on whether you are trying to trap her into saying she sees efficacy in these populations, or she would like you to go look, is that fair?

DR. JOHNSON: Let me just go through. It is the populations, in the words that we are using now, it's the populations in which you might need to go look, but the question is define these populations where washing with plain soap and water or other hygiene measures are inadequate to do what it is that you have said consumer antiseptics must do, which is reduce infection, so where would you look.

DR. WOOD: That lost me completely.

DR. JOHNSON: Maybe I am making it worse.

I think we should stick with the idea that

you answered no to the question that there are existing data which show that any consumer antiseptics benefit any population more than soap and water.

Now, we are saying in what populations would a benefit need to be defined where soap and water or other hygiene measures don't adequately reduce risk.

DR. WOOD: We don't know. I am not sure how you would know that right now. That would be like answering the first question, but backwards again. What we could give you advice on is populations in which it would be worth looking to see if the handwash does reduce risk, but if we know that soap and water does not reduce risk in them right now with the exception of people who can't get soap and water obviously, and then we would have answered the other question in a different way.

DR. PARKER: It seems to me from sort of the practical standpoint that the first thing you do is you wash your hands with soap and water, and

if it is not available, then, you look to the best possible alternative, and so a very useful question I think for me to be able to tell my patients or consumers is, is there added benefit to my using an alcohol-based product or something else after I have used soap and water.

So, if using soap and water is good and acceptable, then, what is the added benefit of using a product after that? To me, that would be a very useful thing to know. I am not sure I know that based on the evidence that we currently have, and then if soap and water is not available, and I am to use one of these alternative products, which populations would that be, are there any populations where that would be a first choice?

The answer to that is no, but is there an added benefit seems to me to be the useful consumer question.

DR. WOOD: Maybe one way to approach this is to take the alcohol sanitizers head-on and say is there evidence that in the absence of soap and water, they would be potentially beneficial. I

think the answer to that is yes. So, rather than dancing around this issue, why don't we address that head-on.

If a consumer is unable to reach soap and water, then, would an alcohol hand sanitizer be beneficial in that setting?

DR. HALDEN: What is a reasonable distance to travel to the next faucet?

DR. WOOD: Well, it depends if there is another faucet.

DR. HALDEN: Yes.

DR. WOOD: We are not going to define that, I will tell you that. But in the absence, assuming there is no faucet within sight, then, is there evidence? We saw evidence that they seemed to be equally effective to soap and water, so in the absence of soap and water, is it likely that they would be beneficial?

I mean that seems to me a useful question for labeling, so should we take that as a question? Would you like a vote on that?

DR. HALDEN: Can I make a quick comment?

DR. WOOD: Yes.

DR. HALDEN: I think it has two components. It's the human side and then the

microbiological side. I think by our vote, we determined that we are not confident right now that either product is better, just soap and water, or the specialized antiseptic lotions.

But I can see a human component where, for example, people have a skin disease or whatever, they can't come in touch with a high pH soap or something, so they would be served by a product.

DR. WOOD: I would be careful about that. We have not seen data for that. I mean I am talking about the situation in which you cannot use soap and water, and so we have seen data that said these drugs were as effective as soap and water, and in the absence of soap and water, do we want to say that that is an indication for their use.

Would that be useful, Susan?

DR. JOHNSON: That would be very useful, and I don't necessarily think that we need to vote, but if you just want to poll what people's

responses are to that. It is built into the question to perhaps separate these out if that's the way the committee saw the data.

DR. WOOD: Let's start with Dr. Halden.

So, articulate what you see as the role for an alcohol-based antiseptic handwashes in the absence of a faucet in sight.

DR. HALDEN: I think that alcohol-based products play a role there.

DR. WOOD: Sonia.

DR. PATTEN: Yes, I agree.

DR. WOOD: Robert.

DR. TAYLOR: Yes.

DR. WOOD: Ernest.

DR. CLYBURN: Yes, and I would go a step further and say not necessarily if water wasn't available. None of us are in an area where it is not available, but even where it is not practical, in a child care setting where you have got 20 kids, and you have got to wash their hands, it makes a whole lot more sense probably to use alcohol.

DR. WOOD: Good point.

Ruth.

DR. PARKER: Yes, useful.

DR. TINETTI: Yes, useful.

DR. SNODGRASS: Yes.

DR. FINCHAM: Yes, useful.

DR. BLASCHKE: Yes.
DR. WOOD: Yes.

DR. ARDUINO: Yes.

DR. OMEL: Yes.

DR. WOOD: Okay.

So, we have taken the alcohol, that bit out now. Do we still need to return to 2(b)?

DR. JOHNSON: We established that the committee voted largely that there was no available data that showed that the washes were better than the use of plain soap.
What other populations do you expect that washing with plain soap and water or other hygiene measures are inadequate?

DR. WOOD: I don't see how we can answer that.
DR. JOHNSON: I think you started on

looking at your patient populations in your practices and said perhaps immune-suppressed.

DR. WOOD: No, you are misunderstanding. I think what we are saying to you clearly is we don't see data in these patients, we would be interested to see such data developed that would convince us that there it was beneficial, but--

DR. JOHNSON: We had anticipated that the committee might have particular populations of interest that they treat or that they are finding or have an opinion on the fact that soap and water was not effective.

What I am hearing you say is that any population would need data, because you have answered no to the question.

DR. WOOD: Right. I see some nods. Yes?

DR. ARDUINO: Because we don't have the baseline data that you are asking for. We don't have data on just plain handwashing with the special populations that even says that handwashing alone increases their risk.

DR. WOOD: Let's move on to No. 3, which

says, "Earlier this year, NDAC met to discuss the efficacy criteria for healthcare antiseptic drug products and accepted clinical simulation testing as a surrogate for bacterial infection rate to measure efficacy of healthcare antiseptics. What types of studies/endpoints should be used to establish efficacy in populations that require consumer antiseptics?"

This does need a bit of discussion, I think.

Who wants to start off with that?

DR. CLYBURN: It particularly needs discussion in the way that we answered No. 1, and that if we say we are going to demand that we decrease infection, using surrogates really isn't adequate to do that.

DR. WOOD: So, develop that a big, Ernest, what would you like to see?

DR. CLYBURN: I mean I think we are beginning to see data on actual infections, and certainly we saw that for symptom complexes. I think direct studies to show decreased infection

rates in given populations.

DR. WOOD: Okay. Any other comments?

DR. OMEL: I would like to see a rather simple study in which they culture hands, use the product. After the hands are dry, culture again. I would think that reduction of bacteria should at least make one think that it is going to reduce infection.

DR. WOOD: That is what has been done.

DR. ARDUINO: There are two problems I think with this way. One is our good, old disinfectant testing by looking at log reduction to actually even say that your special ingredient, whatever you are using, actually works or does something.

But then that has to be coupled with clinical studies to say in real life settings, you know, we have got our surrogate tests that say it does this in the laboratory, but does the product actually work in use situations where you then say it also reduces infection rates.

So, one is kind of a laboratory screening

side of things, and one is like real use of a product.

DR. WOOD: I guess my comment would be that it is not just the endpoint that is the issue here, it is the patient population should use, and to make it reasonable and make the sample size reasonable to do, I would study populations at high risk, and either families at high risk because of an infectious member of the family already present within the home, in a setting where diarrheal illness was prevalent or whatever.

I don't think you could just go out and study healthy, middle-class individuals with 2.2 children, because the ability to demonstrate an effect there would be extraordinarily small.

DR. ARDUINO: I would also look at populations like peritoneal dialysis patients or patients who have catheters.

DR. SNODGRASS: I think you could expand that, any surgical device that breaks the skin barrier, and then looking at those patients.

DR. WOOD: Terry, then Ruth.

DR. BLASCHKE: I think a lot of what this committee deals with then, of course, is as John was saying, it is really the label, how would the

label be written for such a product, and would you then want to select a population where it would sort of fit those criteria that we have talked about multiple times before for over-the-counter products, could they identify the problem, and would the label be written, and that would be part of such a study, as well.

DR. WOOD: Ruth.

DR. PARKER: I really think a very useful piece of information is what is the added benefit because of the availability of soap and water for most, not always, but I think that is an incredibly important thing. That is what I want to know. If I use that, and I do it correctly, what added benefit is there to using one of these products in household transmission of hepatitis A, you know, pick your population, whatever it is, but that would be very useful for me clinically, to be able to say here is a clinical setting, here is a

high-risk, hepatitis is very common, not only should you be washing your hands, but there is added benefit.

That would be very useful clinically, and I don't know that right now.

DR. WOOD: I think that would take a fair amount of work, but it would be possible to define populations in which a sample size would not be overwhelming to demonstrate that.

Robert.

DR. TAYLOR: I think the monograph does--we have already said in No. 1 that we do require clinical benefit in reducing risk, and the monograph already requires surrogate testing.

I think the question that is being asked, is there anything else that we need to add to the requirement. That is the way I see it. And if so, what is it?

DR. WOOD: This should be a question, but I could see you coming up with a study that showed clear and incremental benefit in reduction of infection in some high-risk population, and then

just an off-label use in prescription drugs, that being extrapolated to other high-risk populations, either in people's minds or perhaps with data.

That is kind of where I would see the development going, and that isn't actually a huge task if you picked your populations carefully.

Terry.

DR. BLASCHKE: It may be that one of the challenges that we heard about in the studies that were described this morning, is that the handwash population generally also got instructions in how to wash their hands, and in designing again a real world, real use study as we think about in NDAC, we ought to think or at least allow the companies that might do such a study, not to be required to encourage handwashing anything other than what they would normally do, and then truly compare it to the availability of a bacterial soap or to an alcohol.

DR. WOOD: It might well be that bad handwashes do better with antibacterial soap is what you are saying. That's a good thought.

Mary.

DR. TINETTI: I just have a question, and this is for the FDA. I mean is this going to impact at all upon the labeling and the marketing,

because on the one hand, Alastair, you said that they should really do it in high-risk populations because it would be very hard to see an effect in sort of a healthier middle-class population that is going to do better handwashing, et cetera.

But on the other hand, my guess is that the major users of these are going to be the people that you are saying they probably need to study.

So, I think that that probably has a little bit of a discussion, because the numbers of these immunocompromised people that we are talking about are still, whether it is peritoneal dialysis or immunocompromised, it is still a pretty small part of the market, so I think it probably is worthwhile talking about whether we want to see this evidence in the larger population.

DR. WOOD: Well, it is certainly more profitable to sell antibacterial soap to people with four bathrooms than one.

DR. OSBORNE: Dr. Wood, I just wanted to mention from what I have looked at, it looks like it is difficult to get investigators to evaluate plain soap and water against any other product in a high-risk population.

They tend to bring up that it sounds

unethical to them, because they are leaving their patients at more risk than they consider comfortable.

The other thing I wanted to point out is that one of the studies that was presented this morning, I think does get close to showing the benefit of plain soap and water in reducing infection risk, and that was, if you remember, one of the arms of the Luby study from Karachi, Pakistan, had a placebo soap, and then there was a control group that had just nothing, and the placebo soap showed a lower incidence of impetigo, diarrhea, and respiratory illness.

DR. WOOD: We know that. That is what influenced No. 1.

We will move on to No. 4.

DR. JOHNSON: Could I just ask one question before you move on?

DR. WOOD: Yes.

DR. JOHNSON: We did want you to comment, if possible, on--the first part of that question is that we made the assumption with the healthcare antiseptics, and I think John brought this up earlier, that the surrogates for bacterial infection and the efficacy criteria that we set

were assumed to have some effect on infection in a healthcare setting, because of the high risk in the healthcare setting.

The question here is a little bit are you making the same risk. I think someone down here said that the clinical simulation studies may be acceptable. Can we assume that same paradigm in the consumer realm?

DR. WOOD: I think the point was actually made just a second ago that the data we saw said handwashing was pretty effective, plain handwashing, and there was no data that I saw that was very convincing that antiseptic handwashing was

substantially more effective.

In the March meeting, that data wasn't there, at least if it was, I don't remember it. That is, there wasn't data that spoke to antiseptic handwashing versus surgeons washing with regular soap and water, and so that didn't seem like a very attractive thing to go do, so they were already doing it, and it was reasonable to continue to do that. At least that is the way I felt about it at that time.

DR. JOHNSON: The other question that I would have just to finish fleshing this out is in answer to Dr. Tinetti's question, you had posed a question a few minutes ago about would we essentially generalize from population studies of high-risk populations to the general population. If you want to comment on that, I would just ask you do so.

DR. TINETTI: My guess is that it may be inappropriate to extrapolate. My guess is the industry will extrapolate. If I was in industry, I would extrapolate, but the infection rates are

going to be very, very different, and potentially, the benefits of the different interventions may be different, so I would be cautious about generalizing from one population to another.

I also wanted to comment on your question about the healthcare. First of all, I think we got compelling evidence that it was difficult to actually look at infection rates in healthcare environment, number one, and number two, as Alastair just said, we really couldn't do the comparisons of looking at these antiseptics, so that was I think many of the compelling reasons why we bought the surrogate testing. That is not the same in the community where we already clearly have studies that have studies that have looked at the clinical outcome of interest.

So, I think it doesn't generalize from the healthcare environment to the consumer setting.

DR. WOOD: The other thing, Susan, was we were asked then, now that I am thinking about it more clearly, we were asked to consider reducing the surrogate standards, and what the committee

came down against was reducing the surrogate standards in March because of an absence of data to reduce the surrogate standards.

That didn't mean I think that anyone felt particularly warm and fuzzy about the surrogate standards. It was just they didn't see any reason to reduce them giving that there was no evidence they are right in the first place.

DR. SNODGRASS: The only other comment I would make is that there is an analogy of studies about how high the temperature is in dishwashers and whether you use a dishwasher or a handwash at home, and the incidence of colds, and this is in otherwise healthy families.

Those kinds of studies have been done, and you could something similar. You really need data in the user, who is going to be the user here, and I think those can be designed.

DR. WOOD: Jack.

DR. FINCHAM: I just would encourage similar comparisons, and I really struggled with trying to delineate the difference between clinical

environment versus consumer environment. In my mind, they are all exactly the same. Somebody may be more at risk because of patient factors or disease morbidity, but nevertheless, somebody that perhaps is, quote, unquote, "basically healthy," may be very much at risk even if it's not in a quote, unquote, "clinical setting."

In my mind, this is a setting, period, that is encompassing not only different types of patients, but different environments, and I think that is the way I look at it.

DR. BLASCHKE: I want to play just a little devil's advocate for a moment, and that is, that I think there is evidence in a number of other settings that the size of the inoculum is important, and I am sure that is what has led to the idea of a 2 log versus a 1 log or a 0.5 or whatever. That basic inoculum is important.

I think, Susan, you asked a question earlier whether there is a link between this in vitro/in vivo testing and risk. I think there probably is a link, but it has really not been well

documented, but I think certainly in other settings, inoculum is a very important factor in whether or not something is going to become an established infection.

DR. WOOD: Just going back to Susan's question, I guess the committee did agonize once before over aspirin, and the data there actually speak directly to this, and that the issue, as I recall, that they agonized over was whether a low-dose aspirin in a low risk setting would have the same benefits and risks as it had in some of the clinical trials.

There was not a uniform endorsement, I guess, of that, and so I suppose extrapolating from high-risk infections to low-risk infection rates would be the same thing probably.

DR. PARKER: The only other thought I had relates back to a comment that Wayne made earlier, just about safety implications particularly with perhaps babies or young children, and whether or not there is such a thing as being too clean, oversanitized, and can there be safety concerns on

the far side of that, just to keep that in mind

that is sort of a special population.

DR. WOOD: Are we ready to go to 4 then? Okay.

No. 4 relates to risk. As with many

drugs, the use of consumer antiseptics may be

associated with a number of adverse consequences.

The extent to which these consequences are attributable to consumer antiseptics, and the

importance of the consequences to public health are

varied. How should each of the following be

factored into FDA's decisions about product

regulation?

They go through three. One is application

site dryness, local irritation.

The second one systemic consequences to

the individual consumer, incomplete immune system

development, development of antibacterial resistance in the individual, and then the third

one is the societal consequences with chronic

exposure, and so on, that we talked about earlier.

Let's take each of these separately.

Yes? Sorry.

DR. FINCHAM: Could I just have something

clarified in my own mind? My assumption when

looking at this was that all of these are important and that the agency wants some type of a ranking or an assessment of which is more important than another, and if that is wrong, please tell me.

DR. JOHNSON: I don't think that they have to be ranked compared to each other necessarily. Just an understanding coming into this meeting, we didn't have an understanding of whether the committee would concur or disagree that the kinds of data that were being presented, particularly for risks (b) and (c), should enter into the realm of our consideration.

DR. WOOD: I see. Okay. Then, I think we should definitely have discussion around that.

Let's take (a) first, which is local irritation, dryness, and so on. Does anyone want to discuss that?

Wayne.

DR. SNODGRASS: It is important, but it is

not life-threatening, so I would say yes, it is something you would take into account, but it wouldn't be the top of my list compared to the others we have.

DR. WOOD: I share that. I think it is important although, in fairness, I didn't see any evidence that it was a major clinical issue with these products.

DR. PATTEN: It seems to me this might be an issue for labeling as a possible adverse effect, and then the recommendation is use lotion. If this is the worst of the worst, local irritation and dryness, I think it can be easily remedied on the label, deal with it on the label.

DR. TAYLOR: I guess there is another admonition, and it may be in the label anyway, is where do you apply these things. I mean the assumption is that people apply them to their hands, but there are compulsive people that may want to apply it other places, as well.

DR. WOOD: Do you want to develop that for us?

[Laughter.]

DR. WOOD: So, Robert is worried about the obsessive compulsive who washes all body parts many

times a day.

DR. TAYLOR: That would be all of us.

DR. WOOD: Any other comments? Okay, let's move on to (b). I think (b) and (c) here are trying to separate the consequences for the individual versus the consequences for society as a whole through general changing of the environment. So, let's deal with the individual one in (b) first.

Systemic consequences for the individual user, incomplete immune system development, which is the asthma hypothesis, development of antibacterial resistance in the individual. Concerns? Jack.

DR. FINCHAM: I think based upon what Wayne mentioned earlier, about the case studies of young infants and application of alcohol to an excessive degree, that certainly focuses my attention on it this is pretty important. Even if

those numbers are small, the numbers, in and of itself, are significant to me.

DR. WOOD: So, what you are saying, Jack, I guess is that it would be important to label these products as to which population should not get them, and the dosage, and so on.

The other part perhaps, Susan, that you are getting at here is would you consider it essential that in developing one of these products that you had to demonstrate that you didn't produce an altered flora in the individual.

DR. JOHNSON: I think John Powers said this earlier. If it wasn't you, John, I apologize to whoever did say it. But the standard for drugs is demonstrated safety and efficacy.

DR. WOOD: Right.

DR. JOHNSON: Rather than waiting for a problem to occur and then doing something about it.

DR. WOOD: That being the case, that would be a tough study to do actually. I mean that needs a lot of thought as to how to do that study. I am not sure, sitting here, I can think right now about

how you could have to design that study, but that is an important issue.

DR. SNODGRASS: I would add to that, that, for example, bacterial resistance, to get clinical evidence in individuals, I think that is going to take a long-term kind of study, so that is not going to be necessarily simple or less expensive.

With regard to incomplete immune system development, if the paradigm there is, well, if you have used this excessively, you don't get enough exposure to bacterial antigens, therefore, you have got a lowered immune functioning. I think that would be a very difficult, incredible study to try to do. I can't imagine it being a requirement actually.

DR. WOOD: Well, that is basing an hypothesis that right now is unproven anyway, so I think it is not reasonable to set that as a drug approval standard.

DR. POWERS: If we can clarify for a second, though, we are not necessarily talking about drug approval standards here, so these might

be things that people would do as Phase IV commitments over time.

Many times we approve a drug and then look at postmarketing studies to see if a long-term problem occurs down the line. So, we didn't necessarily mean this in terms of this is going to block anything from being approved, but more in are these things you would be interested maybe in seeing long term, as well.

In other words, the immune system hypothesis right now is a hypothesis, but you have to either approve or disprove that hypothesis down the line.

DR. ARDUINO: So, this is more long-term surveillance. I mean to even see antimicrobial resistance develop, that may be 10, 15, 20 years down the road.

DR. WOOD: I am not as reassured by John's comment as he is. I mean after all, the products have been on the market for a long time. Show me the data you have got that tells me anything about long-term antimicrobial resistance.

DR. POWERS: I think that is part of the reason we are asking. In fact, we have an interagency public health task force looking at

this issue with resistance, and I think it is actually on the public health action plan. It is not up at the top, it's not one of the 13 top items, and to my knowledge, we have very little surveillance data on this, and when the NDAC last addressed it in '97 to now, what do we have to look at?

So, the question is do we want to incorporate this into going forwards and to making this something that we would want to look at. Again, just because we haven't found it, it could be because we are not looking hard enough either, and would that be something we would want to do better.

DR. SNODGRASS: I would put that in the context of antimicrobials in cow's milk and the changes in resistance there, so that is going to be a large population study and a longer term surveillance you would have to do.

So, that is not necessarily tied to one particular product. Maybe the whole category of products, in other words, great antiseptic use here, handwashing use, does that lead to something like this, but that would be a large sort of population study, so I don't know who would fund

that.

I mean you are right, it is postmarketing, but it is maybe in another category perhaps.

DR. WOOD: I mean you would almost need to find families that were all obsessive compulsives and using this stuff all the time and then became, you know, populated by resistant bacteria or something like that.

DR. SNODGRASS: You are talking about longer term. Let's say you have a million people that use this, and there is another million that don't, whatever the products are, and then down the road, a year, two, three, four years, you are able to show there is some general change in resistance to one or more organisms--

DR. WOOD: Good luck.

DR. SNODGRASS: Yes.

DR. HALDEN: This is being done in the European Union with the use of antibiotics in meat production, where we look at the occurrence of antibiotic-resistant strains, so it is not out of the, you know, it's in the realm of possibility, but it sure will require some resources, and it is worth the effort, I do believe.

DR. WOOD: So, the committee is concerned

about the individual user, I think is the message.

The societal consequences associated, is there any more discussion on that before we move on? Yes, Wayne.

DR. SNODGRASS: I think it's an important issue. The question is sort of funding in way. I mean I don't know that this is necessarily limited to the industries per se should be funding it, but rather this may be a societal, governmental issue, or some mixture of it.

From my perspective, yes, that is a very important question. I think it needs to be addressed, but how you go about it, I am not sure

it's in the typical kind of Phase IV postmarketing surveillance. I think it's a little bit broader public health issue.

DR. WOOD: I think it's important, too, but I must say I think it would be an incredible hurdle to put in front of a product. I mean I don't see how even as a Phase IV commitment it could ever be satisfied.

So, I think it's interesting and titillating, but it would be a killer to put into any Phase IV commitment to demand that somebody did that. I mean I am not how one could do it with any credibility without investing huge amounts of money. As people have said many times, not showing a risk is not the same as showing no risks, so it would be never ending trial.

So, I think it's of concern, but, boy, it would need to bite you on the bottom before I would put a lot of effort into it.

DR. FINCHAM: Alastair, I agree. I think this came up in the spring when this was brought up in the context of the other products as far as what

the market share and the market viability of this is, and the Consumer Representative is no longer with us, you know, adequately addressed that.

DR. WOOD: This is different. This is huge, but I think it is just how to do that.

Any other? Ruth.

DR. PARKER: I guess, you know, stepping back from this, I just want to be sure that I am understanding this correctly. I am taking away something different about using the products that were based as sort of this residue/non-residue. There is a difference.

I am trying to be sure that--there may be differences in systemic consequences based on whether or not you fall into one of those categories or the other, and we should look at that. That is really important because I am very concerned about the whole resistance thing and whether or not we are capturing that, and I still am not sure that those that fall into the residue category, I don't even know why we are using them.

That question didn't come up, but I sort

of step back from this and say wait a minute, I wasn't convinced that I even understand why they are out there. I got the alcohol thing, I got the soap and water, but I saw that and I sort of just had a red flag and said, gosh, I hope somebody pays good attention to this, it's kind of got me worried.

So, in a simplistic way, that's what I feel and I want to make sure it's captured somehow.

DR. WOOD: Okay. That's a good point.

DR. CLYBURN: Alastair, can I just point out one of the ways we sort of looked at this is we didn't know how you were going to answer Question 3. In Question 3, you are saying you should establish some clinical benefit.

In the situation where you have some clinical benefit established, is this such a problem that it makes it--they have to answer this question before we could proceed.

DR. WOOD: Right, I see, and my feeling about that, personal feeling, is no, it's not, because if you made it a sine qua non for

proceeding, then, I think you would absolutely kill it. I don't see how it would be doable.

There is not data been produced that this is an issue for individual users right now. That is not to say it's not, but there is no data to show it is. To demonstrate that it is such a risk would be a massive undertaking--I am sorry--to demonstrate with some level of certainty that it is not a risk would be a massive undertaking that I think is an unreasonable impediment to marketing something.

My view would be it is worth monitoring. John sort of addressed that. I have less confidence in John's ability to detect it than he has, but there it is, particularly given the fact that he has not detected anything in 10 or 15 years of supposedly looking.

So, I am somewhat comfortable with wait and see and letting that shake out unless something really came up and hit you with it.

Mary.

DR. TINETTI: I look at it a little bit

different and follow up a little bit with what Ruth was saying. I agree with you, I think to try to find the evidence of harm would be very difficult, so I would sort of turn this around, because really what we are alluding to here is benefit to harm.

If there is the potential for harm, and we can't necessarily detect it, that, to me, would give a higher--you would have to have a higher standard of benefit. To me, that would argue not benefit of these agents against a placebo, but benefit against agents we already know are safe and effective - alcohol based and soap and water. So, to me, that would be one say around the dilemma.

DR. WOOD: That's a good construct.

Does that give you what you need, Susan?

DR. JOHNSON: Yes.

DR. SNODGRASS: One simple thing. Are all soaps the same?

MS. LUMPKINS: In a word, no.

DR. WOOD: They don't smell the same, I will tell you that, and they don't cost the same.

The answer is we clearly don't know.

Let's move on to 4(c). Societal consequences, are we concerned about that? Jack.

DR. FINCHAM: I think there is a hierarchy

of concern. I am more concerned perhaps about fluoroquinolones in water, but I am concerned about this, as well, based upon Rolf's presentation this morning, so I am concerned. I don't know if you want a degree of concern, but I am concerned.

DR. WOOD: I am concerned, too. I am more concerned about estrogens in water, I have to tell you, but what can I say.

I guess the question they want to know is what we would do about it. Maybe I can formulate it, and see how people respond. I mean would you demand that there was zero exposure? Would you demand that such products had to break down before they were flushed? That's to non-toxic products, obviously, and that is one option I guess. I am just taking an extreme position to see how people react to it.

DR. HALDEN: I am not sure whether that is helpful. We always talk about, you know,

degradation, often it's just transformation. Then, you have two, three, four products. You get into proving for every single one. Nobody would do anything about it, and sometimes we have carcinogens.

So, this is a difficult one of breaking down. I think you should start with the type of chemistry that we are confident about, that has a minimum level of risk. Alcohol is a good example because it is broken down by microorganisms by us, and we drink it recreationally, how bad can it be.

But there is other chemicals that we shouldn't ingest or, you know, apply in vast quantities. So, I think it is just a common sense issue.

DR. WOOD: So, that is not something we have not actually raised at all up to this point. You are saying there are chemical antiseptics that will be more and less desirable to be used in large amounts in consumer soaps, because of their chemistry, right?

DR. HALDEN: I think any graduate

environmental chemist coming out of grad school, having absolutely no scientific experience, can look at the chemical structure, can use existing models and predict how these chemicals behave in the environment.

Why do we make such poor choices? After having tried DDT, having banned it, having tried PCBs, having banned them, why are we still working with this type of chemistry? We have proven over and over that it doesn't work. Let's move on to something that we know will break down, that doesn't have harmful effects, that breaks down very rapidly regardless of the conditions we have, whether it is called warm or lots of light or little.

I think it is just common sense. I am not asking very difficult questions here.

DR. WOOD: So, that is the societal consequences of the chemistry, I guess. There is another bucket as I see it here, which are the societal consequences of the anti-infective property of the drug. Do we want to address that,

as well? Dr. Levy talked about it and others.

DR. SNODGRASS: Sure, on the environment.

DR. WOOD: Right.

DR. SNODGRASS: Right. If it's a major tonnage amount, then, at some level, somewhere, it should at least be evaluated and surveyed. I mean there is plenty of examples of that in other kinds of industry where that impact is happening, and you don't necessarily want to be adding to it.

If you have got tonnage amounts that are still available out there, in other words, it hasn't broken down, and there is some persistence, and then you have this other effect on whatever, wetlands or whatever, then, that is something to be put in the equation.

DR. POWERS: Could I maybe ask this question in a slightly different way?

DR. WOOD: Sure.

DR. POWERS: Dr. Tinetti brought this up, which is what makes me think of it. We rarely contrast the degree of benefit to the degree of risk. When we were talking about healthcare

antiseptics, we are talking about people that may, say, get a postoperative wound infection which could potentially be lethal in that patient population.

Here, what we saw today was data on a couple more sniffles, things that are technically not that lethal, although some of those could be, some of those gastrointestinal diseases can be quite severe even in healthy people.

So, the question really, when I think about this, is that potential benefit for decreasing the common cold or a viral gastrointestinal illness, is that balanced by what we may be doing in the long run to echo systems, and that may be one way to think about this.

DR. WOOD: And is that increasing the risk of the person having the severe infection in hospital that is resistant to antibiotics, I mean it actually ties back into that.

DR. SNODGRASS: This gets into what kinds of surveillance systems to put into place, so that you can begin to track those kinds of things to

actually make some valid connections.

DR. WOOD: Yes.

DR. CLYBURN: I guess the other comment, going back to that, is for the two products we saw today that didn't have demonstrable benefit, why continue in a situation where there is potential risk and there is no demonstrable benefit? Why wait until we can track something before we do something about it?

DR. HALDEN: I would like to second that.

DR. PATTEN: My sense is that the risk is more than potential. I mean we have some pretty good data that we saw this morning, that the risk is real.

DR. WOOD: Risk of what now?

DR. PATTEN: Of contamination of the environment, risk to the community at large, the population at large through use of these biocides.

DR. WOOD: I guess the question is, though, finding them there is not the same as demonstrating a risk. I am not meaning to argue that point, but just I think it is important to

make that distinction. Just finding something in whatever doesn't sound good, but it is not the same as demonstrating a human health risk, I guess.

DR. SNODGRASS: But I think there is additional consideration on that. I agree with you, but finding them and then realizing that certain metabolic pathways, reactive metabolites, maybe dioxin-like compounds, then, you are adding other considerations into the equation.

Does this committee want to recommend that two compounds not be on the market?

DR. HALDEN: Let me turn this around. Name one chemical for me that persists in the environment, accumulates in biota, and in the long run has not been questioned and ultimately removed.

Name just one chemical that we feel confident it bioaccumulates and you are just happy with, happy as can be. I don't think you can come up with an example.

DR. WOOD: Probably not, but I guess I am just concerned that we don't create the impression that anything that doesn't degrade or is found in

sludge immediately has to be removed from the market. That would make me very uncomfortable.

DR. HALDEN: Oh, absolutely, because I mean there is element in sludge, there is metals, that they can't go anywhere.

DR. WOOD: I mean organic chemicals.

DR. HALDEN: But what we have here, we have closed the loop to secondary exposure, but other groups have shown that you can detect these chemicals in human milk. I think this is evidence that the circle is closed, and it is an undesirable circle.

DR. WOOD: Let me rephrase it. We have found, for instance, the products of oral contraceptives in water. That doesn't mean to say we should remove oral contraceptives from the market.

Because there is a connection doesn't mean we have to intervene. So, I just think we need to be careful not to go for the top, that's all.

DR. SNODGRASS: Well, you are talking about relative benefit-risk, that's correct.

DR. HALDEN: But there is a difference of having it in sludge and finding it in human milk, for example, don't you agree?

DR. WOOD: It depends on whether there is an effect actually, I think.

Charley, you were going to say something.

DR. GANLEY: I was just going to say with Dr. Snodgrass, it really becomes a benefit-risk issue, and Dr. Tinetti had mentioned it earlier, so if you have a demonstrable benefit, and you are willing to accept some of the risk, and how much of that do you have to define.

But if you have no benefit, and you have unanswered questions about risk, then, they become more of a concern.

DR. WOOD: Absolutely.

Ruth.

DR. PARKER: I was only going to just comment. It mentioned specifically in (c), in the parentheses, this widespread development of antibacterial resistance, and I would just say, though, no, we do not have complete evidence, we

had presentations that there is concern.

I would say from a clinical standpoint that, to me, is terrifying, because as a clinician, that is one of the scariest things I see, and I am seeing it over and over, and when I see something that is potentially linked to one of the most horrifying things I see clinically, it really raises my concern. I don't think we can ignore that.

DR. WOOD: You mean multiple resistance.

DR. PARKER: Multiple resistances and the fact that from a clinical standpoint, that is huge to say that this may be linked. There again, it is back to the benefit-risk, you know, it is back to the same equation, but we are putting it next to something that is so important.

DR. WOOD: So, Charley's point is are we prepared to gamble for development of multi-drug resistance for no benefit or for minimal benefit, and that seems like a reasonable question.

Mary.

DR. TINETTI: Can we, as a committee, make

a statement that we would require the FDA to require studies of benefit of these products over and above the alcohol and soap and water?

DR. WOOD: I hope that is what we spent the day doing, did you all get that?

DR. TINETTI: I think we have been talking around it, I am saying it explicitly.

DR. GANLEY: I think Question 3 was that, wasn't it, that actually said that you wanted clinical--

DR. WOOD: Right, unless you were out of the room, Charley, I thought you got that. I hope we got that, yes. He is absolutely right.

DR. TINETTI: I just wanted to make it explicit, though, that is what we are saying, because otherwise, I think we are seeing a lot of sentiment against it being marketed to the consumer.

DR. WOOD: Secondary exposure to humans, I guess, is the environmental issue.

Anything else? Any other comments?

Then, we are done, and we are done early.

Thank you very much.

[Whereupon, at 4:05 p.m., the meeting was adjourned.]

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