Collaborative on Health and the Environment (CHE)

Environmental Contaminants and Fertility/Early Pregnancy Compromise Working Group Call # 4 Sept. 27, 2004 9:00 am. PDT (16 callers)

ALISON CARLSON: Welcome to the fourth teleconference of CHE's Environmental Contaminants and Fertility/Early Pregnancy Compromise Working Group. We are now officially a working group, by the way, and generally dropping the "Environmental Contaminants" part of the name for ease's sake. I need to remind that this call is being recorded - for my private use only - in order to be able to create a transcript for CHEfertility members unable to be "tele-present" today.

We have two distinguished presenters from federal agencies speaking about their research and involvements relevant to our topic – and we will at the end of this hour hear briefly from CHE's Outreach Coordinator, Jeanette Swafford, about a potential discussion any number of us may want to have about useful collaboration possibilities - but first we'll do a roll-call.

Please announce your name and organization or affiliation if you have one - and for those of you who are on a CHEfertility teleconference for the first time so have never been introduced to the group - please add 20-25 seconds to tell us what inspires your interest in this topic and participation in this discussion-slash-work group: *Robert Rebar, ASRM; Julie Wirth, Michigan State; Ellen Stein, Maternal/Fetal Health for San Francisco County; Jeanette Swafford, CHE; Eleni Sotos, CHE; Frieda Nixdorf, CHE; Shanna Swan, Univ of Missouri; Linda Giudice, Stanford; Edith Eddy, Compton Fdn; Elizabeth Sword, CHEC; Pete Myers, EHS; Ted Schettler, SEHN; Steve Heilig, CHE; Sally-Perreault Darney, US EPA; Germaine Buck, NICHD.*

One quick update: Dr Linda Giudice and I will be facilitating a preliminary Environment and Reproduction Special Interest Group meeting at the ASRM meeting in Phil, PA on October 19th at 6pm in a room TBD [# 407] at the Philadelphia Marriott. We hope any of you attending the ASRM meeting will join us for that meeting.

Our first speaker today is Dr. Sally Perreault-Darney, who did her PhD in reproductive biology at the University of Hawaii, followed by a post doc fellowship at the John's Hopkins School of Public Health. She is Chief of the Gamete & Early Embryo Biology Branch of the Reproductive Toxicology Division of the National Health & Environmental Effects Research Lab at the US EPA. Her personal research interests include toxicant-induced impairment of gamete production and function and its impact on fertility, early pregnancy loss and risk assessment – and the regulation of molecular events associated with reactivation of the sperm nucleus in the fertilization process. She'll be speaking today about her EPA group's body of research and its research priorities going forward.

Before Dr Perreault-Darney starts, though, I'd like to mention she's a member of NIOSH's National Occupational Research Agenda (NORA's) Work Group on Fertility and Pregnancy Abnormalities and a co-author of that group's April 2003 Report in Environmental Health Perspectives titled "An Occupational Reproductive Research Agenda for the Third Millenium." Very worth studying if you haven't already. Dr Perreault-Darney has also delivered a number of presentations relevant to our CHE group's topic in recent years, and I want to note one in 2003 for the Society for the Study of Reproduction President's Symposium on Reproduction and the Environment titled "Tracking Down Reproductive Health Risks for Humans Exposed to Environmental Contaminants. " Another of her presentations was actually a post-grad *course* on "Toxicant Exposure Effects on Sperm and Oocyte Quality" at ASRM's 1997 annual meeting. She is also, I might note, the lead author on that Czech Republic air pollution and semen quality study that Ted Schettler referenced during his science update on our last conference call...

~ **DR. SALLY PERREAULT**: The idea of this Collaborative is fascinating to me. We have a lot to learn cross-discipline, so I am glad to be on this call. I should say that SSR (Society for Study of Reproduction) has just formed an ad hoc committee on the reproduction and the environment, and one of our goals is to try to make sure there is a presence for this topic at the annual meeting.

I've been at the EPA for about 20 years doing reproductive toxicology. Most of our work uses animal models and in vitro systems for studying toxicants. Our division focuses on reproductive effects of drinking water contaminants, pesticides and toxic substances. The last ten years I've made a concerted effort to bridge the animal models with human studies where I can. A collaboration with scientists in the Czech Republic referred to earlier is one of those. We have about 60 people in our division in three different general divisions: developmental toxicology; gametogenesis, for which I am Branch Chief; and endocrine effects. We matrix across that a research program that addresses EPA's programmatic needs for information in reproductive and developmental toxicology.

Interrupt at any time as I march through some of the major projects we're actively involved in at this time. We've had a pretty big initiative in disinfectant byproducts of chlorination in drinking water. Municipalities have to chlorinate our water to disinfect against diseases and so it has fallen to our lab to evaluate if any of these are repro toxicants. It turns out the haloacetic acids and trihalomethanes – these are really small one and two carbon compounds – can be toxic to the testis at high doses and can be carcinogenic. The levels allowed in drinking water now are based on carcinogenicity. We've done a lot of work in animals characterizing them for testicular toxicity. We've used a lot higher doses than you find in water, but the fact that there is toxicity has motivated us to do a human study which is underway. We're collaborating with epidemiologists at the University of North Carolina who are conducting a very large pregnancy outcome study.

We've leveraged a male study off that effort where we're including the women's partners and having them mail in a semen sample. We're analyzing those for standard measures of semen quality: count, shape and motility. We're also looking at some genetic endpoints that would pick up DNA damage that might impact the ability of that sperm to support a pregnancy. It's one thing to fertilize and egg; it's another to make a healthy embryo. So hopefully in six months will have some results on that. We're of course hoping it's a negative study, though we joke about how we love to find positive effects we can publish – but for public health we are hoping that it's a negative study.

The endocrine group has been active over the last ten years addressing environmental endocrine disruptors, including environmental estrogens and anti-androgens. They've been trying to develop better in vitro tests for endocrine active chemicals as have many labs around the world. We're able to prioritize and screen large numbers of chemicals for their ability to bind hormone receptors. If they do bind hormone receptors then they potentially could impact the reproductive system. We have some fairly new in vitro tests now that are being validated and presented to various groups, for example the OECD [Organization for Economic Cooperation and Development], an international body that reviews a lot of test protocols for global use so that big international companies only have to do one test. Scientists from EPA and elsewhere have been active in that, and in fact Congress has mandated that EPA come up with some screens to monitor for these kinds of chemicals in drinking water and foods.

There's another big effort on atrazine which has been in the news a lot lately. We want to understand the mechanism of action of atrazine. It seems to have multiple effects on reproductive function, extending from effects in amphibians to wildlife to laboratory animals. And we've looked at a variety of other xenoestrogens. These efforts are all in response to research needs of the Office of Pesticides and Pollution Prevention at EPA.

The CDC has been monitoring chemicals in our bodies for some time now and they publish their exposures report which is on the cdc.gov website. They are measuring and finding chemicals in our bodies but we don't always know if they are bad. One of those chemicals is called a PFOS, a surfactant that used to be in 3M's Scotchguard, and which is still a lot of water repellants added to fabric and carpets to make them stain resistant. It's one of a whole family of chemicals called PFOAs. And it was surprising to find these chemicals in wildlife and humans. We're concerned about them. Toxicology studies showed when you dose pregnant rats with this substance very late in gestation (the last few days in a rat is equivalent to the last month of gestation in humans), the pups are born looking fine and then they die very quickly from lung insufficiency. So we're studying the mechanism of that and the relative potency of the other members of this class that might be proposed as alternatives. The goal is to characterize their toxicity and try to figure out whether it has to do with the natural production of surfactant in the infant that allows the lungs to expand, allows for breathing. Whether it's actively interfering with that, we don't know – but it's an active area of research for our group.

We have also some long term work grouped under the heading of Human Health Research. Some of it is related to methods development for the National Children's Study. We're seeing if we can use surrogate tissues – meaning we could look at, for instance, blood cells and the genes that are expressed in them to see if we can use blood, rather than sampling organs, to monitor changes in genes that might regulate reproduction. We're also developing methods to monitor breastmilk for chemicals. We're looking at potential effects on children's health later in life.

A related project at EPA is looking at the possible long term effects of exposures that result in low birth weight. In a lot of developmental toxicology studies, normally the only thing seen is that the pups are born with low birth weight and otherwise appear normal. There's an hypothesis based on the work of a researcher named Barker who found that humans subjected to starvation from wars gave birth to babies of low birth weight, and surprisingly when the babies grew up they tended to have problems with obesity, cardiovascular disease and diabetes. It's counterintuitive that being skinny as an infant would predispose you to being fat as an adult, but we are currently doing some research to see if we can develop an animal model for this and therefore establish a link and understand better what the real significance of low birth weight is in a developmental toxicology study.

Another long-term issue these days is that although we do a lot of toxicology on single chemicals, we are exposed to mixtures. So there's a lot of work on related chemicals and whether they have a common mode of action. One family of chemicals under study includes the conazole pesticides. If they have common modes of action, then when you find these substances together in the environment, to estimate risk you may be able to just add those effects. On the other hand, some chemicals may actually compound each other's effects and be synergistic. EPA needs to know this for regulating mixtures that we're exposed to.

So this has been just a brief overview of what our group is up to. These are issues we are actively exploring, and I am happy to answer any questions.

ALISON CARLSON: Many thanks to Dr. Perreault-Darney for taking the time to be on this call. We will let both speakers speak and then open it up for questions if that's okay…

Dr. Germaine Buck Louis earned her masters and doctoral degrees in epidemiology at the University of Buffalo in New York, where she spent 13 years as a professor in Dept of Social and Preventive Medicine in the School of Medicine. She is currently (since 2000) Chief of the Epidemiology Branch in the Division of Epidemiology, Statistics and Prevention at the Nat Inst of Child Health and Human Development. Dr Buck is going through the federal review process now for a *Longitudinal Investigation of Fertility and Environment* prospective study, which she'll be describing today. She is also the principal investigator for two ongoing and quite relevant NICHD studies: one on PCBs, Pesticides and Female Fecundity and

Fertility; and another on PCBs and Risk of Endometriosis and Polycystic Ovarian Syndrome. Dr Buck is Chair of the Fertility and Early Pregnancy Working Group that has been shaping input into the design of the National Children's Study (I don't know if she'll be addressing that at all today – but of course we are quite interested in if/how the NCS might elucidate intergenerational environmental repro effects from fetal exposures). And lastly, some of you will already know Dr Buck's name because she was the lead author of the NY Angler's study published in 2000 in Epidemiology looking at time to conception in women with histories of consuming PCB contaminated fish.

~ **DR. GERMAINE BUCK LOUIS**: I'd like to echo Sally's comment: It is great to be with this group. I won't be addressing the National Children's Study actually, only because I am not the official spokesperson for it within our Institute. That would be Peter Scheidt.

I do want to talk about our *Longitudinal Investigation of Fertility and the Environment* study, which we hope to move into the field in the next few months pending success with the Office of Management and Budget application. We have a very basic goal: To determine if environmental chemicals – we're particularly interested in persistent compounds that most people have exposures to that accumulate over time, and we're interested in the concentrations to which most people are exposed – to see if in fact they impact sensitive aspects of human reproduction and development. We'll be looking at things like some of the flame retardants, some PCBs, some persistent pesticides, and metals. We'll be looking at five different outcomes. Three are reproductive : time to pregnancy, pregnancy loss (including very early pregnancy loss that we'll be detecting with HCG looking for this early marker) and infertility. Two are developmental outcomes: how long women carry the pregnancies – so gestational age – and the growth size of the infant. Most of these outcomes, with the exception of infertility, have been looked at in animal models and to some degree in human populations, but mostly with proxy types of reports like fish consumption and things of that nature. What we want to do is look directly at the concentrations of these chemicals, but also look at them in the context of people's lifestyles. If in fact there are effects that are seen, we can be sure it's due to the chemical and not things like exercise, alcohol, smoking, extremes in body shape.

We are trying to look at how people are actually behaving, how they come to be exposed, and to follow them through the period of attempting to become pregnant. We'll work with investigators from three states, competitively selected through a scientific review process. The three contractors will be Lynn Goldman at Johns Hopkins Bloomberg School of Public Health; Anne Sweeney at the University of Texas, Texas A & M; and Tim Wilcosky from RTI International and the State of Michigan.

We'll recruit couples planning on becoming pregnant in the next six months. About two months from there, we'll enroll them. We'll look at males as well as females. Both partners will participate in a very short questionnaire, which is really only aimed at medical histories for the most part. We'll ask for a blood specimen so the bloods can be sent for toxicology to detect chemicals and metals. Also a urine sample. We'll look also at phytoestrogens – so some of the things that people eat that have been suggested as adversely impacting human reproduction.

Research nurses will then be training the couples in how to use over the counter fertility monitors. We'll ask each member of the couple to complete a short diary that will give us important information about factors that could impact the male as well as the female. We'll ask about things like cigarette smoking, whether the male has an illness or any unusual activity that could increase temperature in the scrotum that particular day. We'll ask the males to contribute a semen sample at baseline.

In month two of the study, we'll ask for a second semen sample. The first semen sample is just as a global marker of whether or not the male is fecund and capable of fathering a pregnancy. In the unlikely chance that we do find someone who has no sperm, we would notify him so he can undergo additional diagnostic work-up and treatment as necessary. The second semen sample is going to be used primarily for the

quantification of the chemicals in semen itself. While we'll repeat the semen analysis on the second, we'll save most of that sample for toxicology.

From the women we'll be asking for two saliva samples. The first one at baseline, we'll measure cortisol to look at stress. It is thought that stress can correlate with infertility, but there is really no empirical evidence to support whether that is true. So we'll collect two saliva samples timed about a month apart, to see if women with a higher baseline stress level actually do take longer to get pregnant or are more likely to have a pregnancy loss – as well as whether an increase in cortisol level over time would be associated with a longer time to pregnancy. Some of the information we'd like to get is whether you start stressing out when you're failing to become pregnant and if that reflected in your body's cortisol level. We see this as some of the first data to support whether or not stress is important in trying to get pregnant.

Based on the limited literature, we anticipate that about 60% of our couples will get pregnant in the first three months, so even though they'll be doing a daily diary for us, it's going to be for a very narrow time period. We're planning things such as looking at the timing of exposures, not just the chemicals but things like cigarettes and alcohol, in relation to where the woman is in her menstrual cycle. Maybe it's okay to smoke cigarettes in the first five days but it's not okay in days 10-14…We just don't know. So what we're trying to do is be able to talk about critical windows. Are there any really important exposure time periods during the menstrual cycle that are really important?

The reason we are asking men to keep a diary is that we're very interested in couple-dependent kinds of exposures. If we see an adverse effect – let's say the couple is taking longer to get pregnant – we want to be able to say if the effect is from the female, or from the male. Who is driving the effect, or is it really the couple?

Once the couple gets pregnant, we're going to ask the women to complete a diary just on a monthly basis. We'd like to do it more frequently, but we're not sure we can sell the amount of so-called burden on the subjects. But it's important to try to capture any other important events that might happen during pregnancy that could impact gestational age or birth weight. It's important to try to know, if there is an effect, if it's the chemical(s) that is driving the effect, or if it is something else.

We're planning to study 800 couples across the three sites, and anticipating that average couples would be in the study for a year. Most will get pregnant within three months and then be in for nine months of pregnancy. That is comparable, because the study is statistically powered to look at infertility. As far as we're concerned, we've been unable to find any incident data on infertility – that is, newly occurring infertility – and so it will be an initial attempt at identifying incident infertility as well. So those couples who don't achieve pregnancy would be trying for 12 months.

We're excited about this study and hope that in four years we'll have some very solid human data to say whether or not these chemicals are of concern – and importantly, if the chemicals are, we want to see how lifestyle or couple behaviors might further impact or lower the effects caused by the chemical. We want to study the things that people can change that may help them to have a desirable outcome.

Q & A/DISCUSSION:

ROBERT REBAR**:** When you collect samples for cortisol, will they be collected same time of day?

GERMAINE BUCK LOUIS: Our budget was very thin for the cortisol, so they'll be prior to rising. We've actually looked at some of the studies that have done multiple cortisol levels during the day, and it turns out that what seems to be driving better prediction of stress measures is the single baseline cortisol. So that's what we'll do, roughly at same time of day. The first baseline one will be the morning after the

baseline interview; the second one will be the first time she hits the "M" button on her fertility monitor, when she begins to try (roughly the next month).

ROBERT REBAR: Obviously if you are doing it just once a day, the argument could be that there is altered circadian rhythmicity…

LINDA GIUDICE: How long is the study?

GERMAINE BUCK LOUIS: The funding for the study is four years. We'll recruit couples in a two year period, allow them 12 months to try to get pregnant, and follow them for 9 months of pregnancy. So the four years reflects the two years of recruiting couples.

LINDA GIUCIDE: And how many couples will you have to recruit?

GERMAINE BUCK LOUIS: We're anticipating we'll enroll 1000, with 20% withdrawal, for 800 couples who would fully the protocol.

SHANNA SWAN: Are these first planners?

GERMAINE BUCK LOUIS: No these don't have to be nulligravita female subjects. We anticipate that about a third of them will be.

SHANNA SWAN: Because their stress could be related to prior failure… How long will you collect urine to look at the HCGs?

GERMAINE BUCK LOUIS: *We're* actually not going to be collecting urines. We'll use the Clear Blue Digital Home Pregnancy Kit, so the women will be testing and it will be coordinated with the monitor. We'll be giving the women good protocols when they need to begin testing their urine. They'll be doing two pregnancy test kits each month.

SHANNA SWAN: Just to throw out an idea: Would it be possible to get a subsample of the women who do collect urine and compare?

GERMAINE BUCK LOUIS: One of the nice things is that we are working with the maker of this monitor, so the monitor will have the algorithm of both the E3G as well as the LH. We're hopeful it will save us having to do the daily urine collection because the monitor is actually going to be tracking the test days, which are for most women 10 days. She'll start testing on day 6 of her cycle, and some women with longer cycles, it could end up being 20 days. We're hopeful we'll actually have those concentrations.

SHANNA SWAN: How many couples will you have to screen to be able to enroll 1000 and then 800?

GERMAINE BUCK LOUIS: We think we're going to have to screen 120 couples for every one that is planning to get pregnant and says yes. In Texas, in the 10 counties along the Gulf Coast that comprise our sites there, we have the population pretty well identified. We're basing it on women of reproductive age 18-40. There are two counties in Michigan and three in Maryland. We're primarily targeting counties where we know that there are demonstrated exposures of interest, but we are also interested in minority and medically underserved populations – people typically not in research, and likely to be more exposed because of environmental injustice issues. A lot of calling and talking to people before we get a positive hit.

EDITH EDDY: Are you going to try to get any information about possible exposures of subjects in utero themselves? In other words, where their mothers were living, what they might have been eating before they were born? Smoking?

GERMAINE BUCK LOUIS: It's a great idea, which we've thought about. Some of the sites have difficulty with the concern now of HIPAA that subjects don't have the right to speak about other subjects, family members…So we decided to forego the in utero hypothesis, hoping that we can categorize well the offspring from this particular cohort who hopefully can be followed.

EDITH EDDY: So 25 years from now, then…

GERMAINE BUCK LOUIS: Right.

EDITH EDDY: I just wonder, though I know you've already thought through and are proposing your study, is there any way to inform it with the possibility of what happened a long time ago?

GERMAINE BUCK LOUIS: I agree with your point. It's an important question. We face two issues: a very practical set of demands that are levied upon us concerning what is reasonable to ask subjects to do, how much burden we can impose, and we're already concerned about this study in that regard according to the calculations of the federal government. The second thing that I have to keep thinking about is that we really don't know what these chemicals are doing. There's a lot of conjecture. There's really good animal and wildlife data that say we should be concerned (and I am in that camp). So in answer to this question, what we see the contribution [of our study] being is whether or not these chemicals are of concern…If they are, then there is a whole series of next questions: How did you get exposed? When did you get exposed? How do we ameliorate exposure? Right now, though, we are not even able to go past birth with these children. So in a way, we are a bit stuck, unless we find effects and the children can continue to be studied. So I welcome your question, but we are just not able to do it.

TED SCHETTLER: You didn't mention which specific pesticides you'd be looking at, but among the classes of chemicals you mentioned, you said they'd all be persistent. This raises the question of whether we are continuing to look at chemicals that we know we are concerned about and already doing some things (or know we should do things) to ameliorate exposures…Are we continuing to look at the same suspects? Following on that, it is really tough to look at non-persistent chemicals, but unfortunately those could be bad actors as well. Another question is whether or not there would be any opportunity to look at polymorphisms in subpopulations within this group, because that may well be relevant, and I am thinking particularly in terms of gestational age and birth size. And a final comment is that this is going to be a real statistical challenge because of the multiple comparisons you'll be undertaking on outcome and on exposures…

GERMAINE BUCK LOUIS: You are absolutely right, and when you think about the number of compounds too…We have a great analytic plan that we've developed for the protocol that we stand behind, which is responsive to outliers, the multiple issues, the potential interaction issues, as well as how we begin to think about all these analytes. We *are* interested in the persistent organic compounds. I can tell you that we got public comments back during the 60-day OMB notice about the study and some public concern that we need a lot more specimen collection than we could even remotely begin to approach as far as our funding goes, not to mention the human burden element. The difficult thing for government researchers is that we have to count every second that subjects have to do something in a government study, so multiple urine specimens for some of the phthalates and things like that were something we had to drop. However, I would argue that for a lot of these compounds, while we think they are of concern for children, the effects on human reproduction are really under studied. Certainly time to pregnancy, early pregnancy loss…other than one study, there's no data out there. We need to capture those endpoints as well as those that have to do with children.

I can give you an example of some of the analytes with regard to pesticides: things like oxychlordane, T-nanochlor, DDT and DDE, mirex are the ones I can think of off the top of my head. And we'll be looking at PFOS too – as you know there is no data in that category of compound for the most part. A host of the phytoestrogens, and cotinine.

SALLY PERREAULT-DARNEY: Ted's question was well-put because when we're dealing with environmental exposures to low level chemicals we may not see something across everybody, but if you could understand the susceptibility factors such as those conferred by polymorphisms, it certainly would help. In the drinking water study that I described, we were just able to add a component to map our samples for DNA analysis on selected genes that are involved in the metabolism of CBPs [chlorinated byproducts] . We hope that will give us a hint about responders and non-responders based on genotype. But our exposures with these CPBs are hard to measure because they are not persistant – they clear very rapidly. So this is an association study based on drinking water consumption, bathing habits, and municipal drinking water data. I think we will start to see more studies including polymorphisms in the future. I hope so.

SHANNA SWAN: For Germaine, are you going to look in your study at the sex of the children in relation to the exposures?

GERMAINE BUCK LOUIS: Yes, we will be doing that…

ALISON CARLSON: If there aren't other questions for Dr. Perreault-Darney while she is still on the call, I'd like to shift a bit and check in with you, from a more global perspective interest. This CHEfertility group is obviously very interested in relevant research specifics, but it but has various other interests too. One is ways that members might advocate for enhanced research agendas and funding, for instance, and how we can engage physicians…So I am curious: as you've presented in various arenas, such as medical schools, professional societies, etc, how did you gauge reaction to your presentations from clinicians in general?

SALLY PERREAULT-DARNEY: The clinicians in my experience are quite a different audience from environmental scientists. I'm active in the American Society of Andrology, a small society studying male infertility, and we're trying to make our programs of interest to both the clinical and the basic side. One of the challenges in environmental studies is getting clinicians to understand that we're not trying to predict the fertility of individuals. We're trying to look across a population at what might be associated with fertility. For example, if we find that a group of exposed men has a 5% decrease in sperm count, and it's statistically significant, a lot of clinicians will dismiss that and say that it is biologically not relevant. For an individual man it may not be; but for a population it is because it shifts more men into the subfertile range. So I try to make these points when I speak about toxicology data to a clinical audience. Our objectives are related but not quite the same. Clinicians are interested in asking about patients who are worried about their exposures and what the clinicians should tell them. That's a very different question and hard for us to answer.

[AC: Note Dr Perreault-Darney touching on the reality that repro tox, repro bio, repro epi and repro med all have particular paradigms and languages, as CHEfertility member Patricia Hunt has emphasized in previous calls. This prompts suggestions of the potential benefit of creating bridges between disciplines so that potentially related but differently framed data can be translated and tied together where appropriate. CHEfertility would like to do this kind of bridging, through teleconferences as well as a Stanford co-sponsored workshop and other efforts – and by encouraging the establishment of and then collaboration between, for instance, the environment special interest groups of the American Society of Reproductive Medicine (which has large clinician constituency) and the Society for the Study of Reproduction (large basic science and repro biologist membership) …]

ALISON CARLSON: Another global sort of question: Several of us in this group take an interest in the dearth of organized infertility rate tracking. In some of the smaller European countries where they are better at tracking, there may be some decent data. In the US we have the periodic National Family Growth Survey, but I am surprised at the lack of any very organized or well thought out tracking and original source data. I wonder what the speakers' thoughts are about how we might take a look at these questions and support efforts for better infertility disease tracking – if you've given any thought to this?

GERMAINE BUCK LOUIS: By incidence I mean newly occurring disease. The NFSG data are all prevalence data, crossectional data at any point in time. Prevalence is really a function of incidence and duration. So, there really are no incidence data, at least none that I am aware of, actually even in the world. Even the European data for the most part are prevalence, and there are some nice papers that address how sensitive prevalence figures are to what you choose to put in the numerator and denominator…the criteria, the operational definition of the word infertility. It can be as low as 3% in a population to 34% if you ask women over the course of their lifetime if they ever had any problems with getting pregnant. So it's very sensitive. But in terms of following a cohort of couples to see how many are truly infertile, there really are no data. Certainly none we've been able to find.

There have been a couple of commentaries in the American Journal of Epidemiology by Scandinavian and UK colleagues arguing that we really need to do surveillance of time to pregnancy. Again, this is only for people who are actively trying to get pregnant. But time to pregnancy would be a good screening endpoint to measure threats to human reproduction. And to get a real handle on just how long does it take. If you think about it, while we think we know what that distribution looks like, much of the world's evidence is for white women and couples. There is far less on anyone else. The most recent version of NFSG at least breaks down by Hispanic ethnicity, so we have a little bit on that. But we don't know what the distribution really looks like when he's a little off or she's a little off. We only have a one-size-fits-all distribution. So I'd be *very* supportive of any initiatives that would try to help us get a better handle on problems of infertility.

SHANNA SWAN: The only data I know of on incidence would be the small intensive family planning studies like Bonde's in Denmark. But these studies are so small. And then you have the possibility of a large selection bias, because, as you said, you have to screen 120 couples to get one couple eligible and willing to participate, so how are they different from those who do not participate, and are they representative with respect to their fertility?

SALLY PERREAULT-DARNEY: It's also confounded by the fact that at least in this country many people turn to assisted reproductive technologies after less than a year of trying, so if you go to fertility clinics to try to get this data, there's been intervention before you can really say how long it's taking.

ROBERT REBAR: Actually the US has a much lower incidence of using ART than do other countries in western Europe.

SALLY PERREAULT-DARNEY: The CDC data indicates that almost 1% of births in this country are by ART. That surprised me. What is the European figure?

ROBERT REBAR: I don't know that data, but I do know that their usage is 3-4 times what ours is.

ALISON CARLSON: Out of respect for time allotted for this call, I need to say thank you to our speakers, and let them sign off the call if they need to do so now. We are going to turn to CHE's Outreach Program Director, Jeanette Swafford, for a brief few minutes to speak about the possibility of a separate discussion for self-selected members of this group about potential collaborative efforts that could move our mutual interests forward.

JEANETTE SWAFFORD: I work with the health-affected patient groups within CHE. In this third year, we are seeing a lot of health groups come together to make change happen in a particular disease area. For example, the Learning and Developmental Disabilities Working Group led coordinated efforts on mercury legislation (as well as PBDEs) with groups from across the country. Last week, within CHE's new Cancer Working Group, some of the health groups like the Brain Tumor Foundation and the Breast Cancer Fund, demonstrated a high level of interest in working in areas like biomonitoring and health tracking. Some of these areas could be of interest to infertility groups. To be clear, CHE never speaks for anyone – and each disease area and/or organization has its own culture and sense of what's appropriate and necessary for advocacy, but CHE is willing to "set the table" and provide a platform for groups to collaborate so there can be a greater impact in the infertility field or the women's health field. So I'd like to gauge the level of interest to see which groups among CHEfertility would be interested in a discussion of collaboration possibilities. Some ideas might be to coordinate efforts to support national disease tracking work; or disease registry work; or look at international infertility issues…

LINDA GIUDICE: Are any reps from the patient groups on?

[Because representatives from the infertility patient groups turned out not to be on this call, we decided to try to schedule an early 2005 teleconference for CHEfertility NGOs interested in discussing potential collaborative efforts to promote protection of reproductive health and greater dialogue and awareness about environmental factors in infertility, among other possibilities.]

ROBERT REBAR: I would remind everyone that we at ASRM have an Office of Public Affairs in Washington that can help with these efforts.

ALISON CARLSON: That is wonderful. Thank you. As we've arrived at the bottom of the hour, I need just to get a feel for scheduling of our next teleconference. We'd like to shoot for the week of December 13th if possible, but try a Wednesday this time around for those who have difficulties with Mondays. I will get back to you all on a final next date. Thank you for participating today.

[NEXT DATE HAS BEEN SET: WEDNESDAY JAN 5, 2005 @ 9-10:00 am. PACIFIC TIME. MORE INFOMATION TO FOLLOW]