other stuff saying troglitazone/liver failure, do liver monitoring.

This patient presents to the emergency room with symptoms of hepatitis. She gets sent home with a diagnosis of a viral illness, continues on her troglitazone, no liver enzymes were done. She comes back to the hospital two weeks later with liver failure.

And then finally, a fractionation of patient care that we have patients who were seen by multiple doctors who are managing different aspects of the patient's medical conditions, and this leads to sort of breakdowns in the system. People drop the baton. One person gets the test. They don't send the result to the other person, and the patient can continue on the drug with abnormal liver enzymes.

The next slide, please.

In this slide, I want to focus now on the issue of enzyme monitoring and rapid risers and is liver failure predictable or preventable. We had data on the time course of enzyme changes for 12 patients. In nine of these 12 cases with enzyme data, 75 percent, the transition from normal to irreversibility occurred within a range of four to 34 days.

For most, the time course of liver enzyme

change is unknown. The question is: are these people with the unknown time course, are they rapid risers or are they slow risers? Can we prevent it or is it pretty much unpreventable?

Would they be prevented by the current monitoring or by more frequent monitoring, say, weekly monitoring?

We don't know the answer to any of these questions. We compared the group of rapid risers with the group of non-rapid risers for all clinical characteristics that we could abstract data from the case report forms, and in none of the clinical or demographic features was there any difference between the rapid risers and the unknown risers. In other words, they are clinically indistinguishable from the rapid risers.

So this raises concern in our minds that the majority of unknown risers may also be rapid risers, and this has implications for any consideration of a monitoring program.

Clearly, monthly monitoring would miss the rapid risers who comprise 21 percent of the cases that we have in our series, and the concern we have is that monitoring might miss upwards of 75 percent, or three-quarters of all cases if these prove to be rapid

risers as well.

Next slide, please.

We'll now talk briefly about under reporting of cases because that is an element that we are dealing with here.

This slide summarizes reports from the literature in which serious or fatal adverse drug reactions have been studied to see what is the completeness of reporting. On average ten percent or less of serious or fatal adverse drug reactions were discovered to have been reported.

Of note, even fatal INH hepatitis, which is well known and well described, only ten percent of cases were reported in the study. In that study where that ten percent figure was obtained, they believed that they actually under ascertained the actual index cases of hepatitis by a factor of twofold, which would bring the reporting rate down to actually five percent.

Next slide, please.

The idea has also been proposed by some that the reporting of acute liver failure with troglitazone is more complete and that actually it may be totally complete because of publicity created by "Dear Health Care Professional" letters and by media

attention.

This slide is a scatter plot of every case of acute liver failure reported to FDA. It plots the date of diagnosis of acute liver failure on the X axis against the reporting date, the date that FDA received that case report.

We also have shown sort of two bellwether times. This is the December 1st "Dear Doctor" letter, and this is the July 28th "Dear Doctor" letter, and then we have the same thing on the Y axis. This is the December 1st "Dear Doctor" letter. This is the July 28th "Dear Doctor" letter.

Important features to note in this slide is that there has been a steady stream of cases reports up through the end of the period that we're reporting on. There has been also no apparent clustering of cases in any given time period.

Where publicity has been looked at and studied, it has been found that there can be a very short-term boost in reporting that follows a publicity event. The duration of this publicity effect is less than a month.

If we look at this slide and we look at the time periods of the "Dear Doctor" letters and the associated publicity with them, let's go back to

December 1st, 1997 and look at the time period right before. We had cases getting reported sort of within the month before that, and look at the month after. We don't see a burst of reports.

Now, let's go to July 28th. We have some reports after, and look at that. Look at all of the publicity there. This is two months before a case came in.

The fact is we do not see evidence that there is substantial publicity effects.

One additional point about publicity. Where it's been studied, the reports that come in are consumer reports. They're from the people who experienced these adverse reactions, but it's not from their doctors. It's not the doctors reporting the adverse reaction. It's consumers.

If you look at the case reports of acute liver failure, less than ten percent of our case reports are from consumers. Over 85 percent are from physicians, and the remaining percentage are from allied health professionals.

So we conclude from this that there is no evidence that publicity has stimulated the reporting of cases of liver failure with troglitazone, and so we believe that the reporting rate for troglitazone is

probably in the neighborhood of about ten percent, and near the end of my presentation I'll give additional data that supports that belief.

Next slide, please.

I now want to shift gears. We're going to stop talking about individual cases, and now we're going to put on our population hats, and we're going to start talking about the epidemiology of acute liver failure with troglitazone, and we're going to start talking about things like rates and risk, and so as we go along, I'll try to educate you if you don't already know these things, and please don't interpret that I'm trying to talk down to you. What I'm about to talk about is very complicated, and it all deals about time.

Time is the key to understanding toxicity, liver toxicity, with troglitazone. So keep your eye on time. Time is the answer.

Next slide.

The methods that we used to estimate the risk of acute liver failure with troglitazone. One of the methods was we used a standard life table analysis. In a life table analysis, you do that because not all patients stay on a drug forever. You have some patients that stay on a drug for one months,

others for two months, other for three months.

In the sponsor's own clinical trials, we had only 45 percent of the patients out of their whole NDA who stayed on the drug for six months or longer. So most of the patients in the NDA were based on data of patients treated for five months or less.

So what's necessary then, you do a life table analysis to account for the fact that people don't stay on the drug for comparable periods of time. You have to think of time now as the denominator, not numbers of individual patients, and a life table allows you to do that.

We use the pattern of troglitazone usage from our United Health Care database to pattern the use of troglitazone in the entire United States, and then we calculated the rate of reported acute liver failure for each separate month of drug usage, and this is important. This is what we call the interval specific hazard rate. A rate incorporates the idea of time. It is the number of cases that occur in X amount of patients over X amount of time.

A way of thinking of it is X amount of events in X amount of person-years. So the person-year is now the denominator. It's taking the number of people over the amount of time.

Next slide, please.

Okay. This slide presents the life table analysis. It's based only on cases reported to the FDA. It is not adjusted for under reporting. I'll orient you to the slide.

The left column shows the duration of troglitazone use in intervals expressed as months of use, and we have cases reported as far out as eight months of use on troglitazone.

For each of these intervals of time we calculated the number of patients who were treated in that interval and the amount of time that they contributed to the overall model of risk. From that we could calculate an interval specific hazard rate.

We have chosen to use as a reference point rates expressed per million person-years, and the reason why we do this is because the background rate for acute liver failure of idiopathic cause is one per million per year. That's the risk of being struck by lightning in the next year in the United States. That's the U.S. risk. It's one per million per year, and that's the background rate for acute liver failure in the United States.

So one can look at these interval specific hazard rates and just based on case reporting by

itself, not accounting for under reporting, can interpret this as a relative risk, or you can just look at it as an interval specific hazard rate.

Then we have our last column, which is the cumulative risk. What this demonstrates, it's expressed in terms of one case per how many users in that interval. So, for example, in the first interval where we had all 1.23 million people who have been treated with troglitazone, where all of them got the drug, how many cases did we produce? You know, we had five cases in that group. That gives you one case per 209,000 people in that first month of use.

But it translates to an interval specific hazard rate of 56 per million person-years which, as I've said before, is over 50 times higher than the background rate.

Now, the thing about hazard rates is that the longer you stay on a drug, the longer you accumulate risk. It's kind of like compounding interest. Well, the longer you stay on troglitazone, the more you compound the interest of developing acute liver failure, and that's expressed in the cumulative risk column.

And so what we see here is that during the first three months of use with troglitazone we have a

fairly stable but elevated risk, and then in months four, five, and six the hazard rate nearly more than triples, up to a peak of 185.

By this time, however, if you remember from the slide that I showed earlier of the pattern of troglitazone use in the population, the number of people who are still on the drug is down like now below 30 percent of all people who have used the drug. So we're getting really small denominators, and so confidence limits start to get increased.

Confidence limits tell you how certain are you of your point estimate, and the point I'm trying to make is that although the point estimates seem to drop here, the confidence limits are such that these rates are completely compatible with the rates staying at the level of the peak rate that we've described here.

Under no circumstance, however, is there any evidence that the risk declines. We see no evidence that the risk stops. We have cases reported out to eight months. We don't have cases reported of liver failure out beyond that. We do have cases of severe hepatitis that have been reported to us as far out as 16 months, and in the sponsor's own NDA clinical trials, they had patients out as far as 18

months who were withdrawn from the study because of elevated liver enzymes. I think I misstated that -- who had liver elevations that were more than three times the upper limit of normal.

They ran into the same problems with their studies that we run into here. You've got that shrinking denominator of people who are at risk to experience the event far enough out in time. So you've got to keep your eye on time. Time is the answer.

What we see here is that the cumulative risk increases so that by the time you get out to eight months on the drug, based on case reports by itself, the cumulative risk is one in 15,000 individuals treated with the drug. That's accounting for no under reporting.

Let's go to the next slide, and we'll see what the impact of under reporting is on cumulative risk. This slide is slightly mislabeled, and I apologize for that.

What we mean here is the level of actual reporting or the efficiency of reporting. So cross out the "under," and what we're showing here is what would the cumulative risk look like in the patient population treated with troglitazone at three months,

six months, or eight months of use if the reporting efficiency is 25 percent, that is, if we've received 25 percent of the cases. This would be an exceptionally high reporting rate in our estimation.

If ten percent of reports were received, this is the column that would apply. This is the number that we believe most accurately describes reporting with troglitazone, and then I've shown five percent because there was a survey of Rhode Island physicians that found reporting less than three percent of serious hospitalized or fatal ADRs, and what's beautiful about that study is that they showed that Rhode Island physicians were identical in their pattern of reporting to physicians in the United States overall. And so it's not inconceivable that the reporting rate could be as low as five percent.

In any event, let's just pick one cell on the slide, and I'll explain to you what it means. Let's take this one.

A patient on troglitazone for six months of use, and what this slide suggests is that based on the models of hazard rates and cumulative risk and adjusting for under reporting, that one in 1,800 patients may have experienced acute liver failure.

I'll present additional data subsequently

that will show how this rate estimate is very consistent with the data which we have from population based sources.

Next slide, please.

This slide finally is intended to give a visual display so that you can understand the interplay of hazard rate and cumulative risk. The hazard risk is the upper line. It's plotted on a log scale along the right side Y axis, and we've got rates that go from about 50 up to 185, close to 200, and you can see the time course by time out to eight months.

Along the left-handed Y axis we've plotted in a linear curve the cumulative risk, and this is expressed per million users, and what we see is a steady increase in risk, and I don't have a ruler here that I can display, but it looks pretty linear to me.

The question is the hazard rate shows on sign of decreasing. The cumulative risk continues to rise. The longer you stay on troglitazone, the higher the risk you accumulate. The question is we know maybe what's happening out to eight months. What happens to the person who stays on troglitazone for 12 months, for 24 months, for 36 months, for ten years? We don't have the data. We don't have the answers. We have this. And what we see isn't reassuring.

Next slide.

I'll now explore population based data which we have to try to come to grips with what the level of risk is that we may be dealing with with troglitazone for the development of acute liver failure.

Next slide.

This slide summarizes population based epidemiologic studies that provide information about what the background rate for acute liver failure, idiopathic acute liver failure is in the United States. Here causes such as viral hepatitis, acetaminophen overdose, and other recognized causes of acute liver failure have been removed, and then what remains?

The slide is sorted in terms of size of the study, in terms of how many person-years of observation were present in the study, and the larger study found a point estimate of close to one per million person-years for idiopathic acute liver failure.

A number of other studies failed to find any cases, but that's more a function of their lack of statistical power to detect a rare event.

If you were to summarize all of these

slides -- and I'm only doing it for instructive purposes; I'm not trying to present a meta analysis here -- the rate would be under one per million per year, but we believe that the background rate that we're working with is probably in that neighborhood, one per million per year.

And I would remind the Committee that that is similar to the risk of being struck by lightning in the United States over the course of a year.

next slide, please.

Before discussing this slide, I'll just mention that from the United Network on Organ Sharing we also received information through review of the literature on rates of transplantation for drug induced acute liver failure, and the rates on a population basis for transplantation from drug induced acute liver failure is .1 per million person-years. Okay?

So we've got a background rate of one per million per person-year for all acute liver failure and a background rate of transplantation for drug induced acute liver failure of about .1 per million per year. So those I think are very sort of complementary.

Okay. Now, in this slide we summarize

population based data on the risk of acute liver failure with troglitazone, and I'll need to spend a lot of time on this slide. So bear with me.

We summarize a number of different studies that have information that bear on the subject. The number of individuals in that study are shown in this column, and then the proportion of patients in each study that had six months or more treatment with troglitazone is shown here.

The reason why I have included this is because we don't know what the power of these studies are to find acute liver failure. We do know from the hazard rate information that we've developed that the rate seems to peak at six months and then may continue at that high level beyond that.

So it seemed to us that using a benchmark of six months or longer of treatment would be at least a crude indicator of a study's power to detect acute liver failure if troglitazone causes acute liver failure at the kind of rates that we're talking about.

We then also summarized the number of person-years encompassed in that study, and what I'd like to point out here is the whole thing about time. You can have a lot of patients, half that amount of time. You can have a lot of patients, but not a lot

of time.

Look at this. Sixteen hundred patients, less than 400 years of person-time. You can treat 5,000 patients for two months and not see acute liver failure, and that study in terms of the value that it contributes is almost uninformative because it doesn't have the power to show the effect. If the effect happens later and you don't look with substantial power later, you're not going to find the problem.

Okay. Now, let's go and look at each of the studies. From the NDA they had 2,500 patients, about 45 percent at six months or longer, 1,400 patient-years. There were no cases of acute liver failure that were identified in that study. So you get a point estimate of zero.

But the important thing to focus on when you're dealing with safety isn't the point estimate. It's the upper bound of the 95 percent confidence interval.

This Committee is most comfortable and most familiar, I am sure, in dealing with issues of efficacy. When one concentrates on efficacy, you focus on the lower bound, the lower 95 percent bound of the confidence interval, and you do that because you want to see is the effect we're seeing with this

drug distinguishable from whatever you're comparing it to, whether that be placebo or another drug.

But what you're looking at is the lower bound because the lower bound is what tells you about statistical significance.

When you're dealing with drug safety, you've got to flip and reverse. You've got to look at the upper bound. You have to think of it in terms of what is the capacity of this study to rule out a particular level of risk.

When you do that what you see is that this NDA lacked the power to rule out an incidence rate of about 2,600 per million person-years.

If you further dissected out this study and focused on just the patients who got six months or longer therapy, you would see that the study lacked the power to rule out a relative risk of almost 6,000 per million person-years.

In other words, what I'm saying is although the NDA found on cases, it's more a question of a lack of statistical power to do so. It's not evidence of a lack of an association with acute liver failure and troglitazone.

Now let's go to the next two studies that have been -- these first three studies, by the way,

are familiar to the FDA and have been reviewed by the FDA. We've received information on them. The studies that I'll talk about at the end of the slide, the data have never been presented to the FDA. They have not been reviewed by us. The first time that we saw them was in the sponsor's briefing package to the Committee, but I've listed them here so that I can discuss and instruct the Committee in ways they need to evaluate these studies to understand risk.

We'll now move to the diabetes and prevention program study, which is done by the National Institutes of Health. This study was looking at patients with impaired glucose tolerance. So these are patients who aren't yet diagnosed with diabetes, but they're patients who are at higher risk of developing diabetes.

One of the arms in that study was an arm treating patients with troglitazone. So they had patients with impaired glucose tolerance being treated with troglitazone. Five hundred and eighty-five patients were enrolled in that clinical trial. Eighty-six percent of those patients had six months or more treatment. So you can see there's a real contrast there in a sense in terms of study power.

You know, they've got a lot of patients

who had exposure at the time when the risk sort of goes up the highest.

Person-years were about 580. On average, the patients in this study were treated for a year.

They had one case of acute liver failure that resulted, and that translates to an incidence rate of about 1,700 with an upper confidence bound that goes up to about 9,500 per million person-years.

Now, remember when you're thinking about this incident rate per million person-years, the background rate is one. So this number, this incidence rate is actually an estimate of the relative risk. That upper bound is an estimate of what the relative risk might be that this study is not capable of ruling out.

Then we'll go to the third study, the REACH study. This is a postmarketing study done by Parke-Davis studying the use of troglitazone in patients with Type 2 diabetes. This case produced a patient with acute liver failure when about 2,400 patients were enrolled in the study. The company was kind enough to provide us with information on the time of enrollment of patients in that study or at least the number of patients in the study, and we had to make assumptions about how patients were enrolled. So

we made the simplest assumption one can make, which is that patients were enrolled in a continuous fashion over the time period that the study occurred.

If one does that, we arrived at an estimate that about 17 percent of the patients in this study were on drug for six months or longer at the time this case of liver failure occurred.

The total number of patient-years acquired in that study by that time point was about 780. The incidence rate from that study would be 1,274, with confidence bound that goes up to about 7,000.

We'll now talk about just two of a number of studies that the sponsor included in their briefing document. In their briefing document, they present a lot of studies, and they combined them. Here we've taken a couple of individual cases, studies, and we showed them individually, and we do this because it's more appropriate to look at individual studies than to group studies where one wasn't originally planning to group them.

So we don't believe that a meta analysis is the way to look at that. You lose certain information when you combine the data. You lose information about what the actual power of a study was to show an effect.

So the appropriate way to look at any study that's done to look at the risk of acute liver failure with troglitazone is to look at the study by itself, to look at the power that study has, to identify the problem we're interested in, and then what is the upper 95 percent bound on that study because that tells you what relative risk that study is consistent with.

A study from Glaxo was included int he submission that had 3,000 patients. We have no notion of what the demographics of use were, the duration of use. We know that the total person-years was about 1,200 person years. That would work out to less than five months per patient. So clearly, this percent mark, this unknown is less than 50 percent. It's probably in the neighborhood of 30 to 40 percent, I would guess.

No cases occurred, but what's the upper 95 percent bound? It's 3,000. This study had the bulk of the patients the bulk of the time at the place where the hazard rates were lower and hadn't moved into that period where the hazard rates get higher.

Now, let's go to Sankyo study, 1,600 patients. These patients were treated on average for under three months. So, you know, the percent that

are on it more than six months might be one percent. I mean we don't know.

No cases got produced, but look at the upper bound. It's like nearly 10,000. So the take home message from this slide is that we have some population based evidence from clinical studies. I mean both of these things were basically randomized clinical studies. DPP was a randomized clinical study that had monitoring and baseline testing and everything else. REACH was a randomized study. it had monitoring, baseline testing, and everything else, and lightning struck twice, here and here.

We had these other studies. They're not powered sufficiently to see the problem. They are all compatible with and all consistent with the rates observed in this study. You have to look at the upper bound.

Next slide.

I'll now present data on liver enzyme monitoring and severe liver injury in patients treated with troglitazone from the United Health Care database.

UHC is a health care management company with health plans in nine different states across the U.S. It maintains a research database covering 3.5

million people. It collects computerized data on prescriptions, diagnoses, lab tests, and procedures. It does not collect data on the results of lab tests.

FDA has a cooperative agreement with the United Health Care to conduct postmarketing drug safety studies. We use this database to study enzyme monitoring and the occurrence of severe liver injury in troglitazone users.

Next slide.

This slide outlines the criteria for inclusion in our enzyme monitoring study. We require that all subjects in the study have received troglitazone and have at least 90 days in the database before that first prescription to be included in the study.

The reason why we did this is we wanted to be sure that patients who we saw as a first prescription of troglitazone in our study were, indeed, receiving their first prescription.

The other criteria we had was it related to disenrollment or the end of a study interval. If the time point came where a liver test should be done and that time came after the time point when a patient disenrolled because they changed insurance plans or after a time period when the study interval ended, we

didn't count that patient in the denominator for calculation of a rate at that time point.

Next slide.

This cartoon helps to graphically demonstrate the design of the study. We've got March '97 when troglitazone came on the market up through about October 25th when the first "Dear Doctor" letter went out alerting the health care community about reports of liver failure with the drug.

Any patient who started troglitazone during this time period and who met the previously described enrollment criteria were included as cohort one. About 2,300 patients were included in that cohort.

We then created a second cohort out of all troglitazone users. That is bracketed by December 1st, 1997. That's the date of the first "Dear Doctor" letter that recommended very specific monitoring requirements, and we included in this cohort any patient who started their first troglitazone prescription was between that date and the end of June of '98. Cohort two has, as you can see, about 2,800, 2,900 patients.

Cohort three is comprised of all individuals who started troglitazone and met the other

enrollment criteria from August 1st of '98 following the July 25th "Dear Doctor" letter through the end of December 1998, 1,400 patients in the final cohort.

Next slide.

This cartoon demonstrates the analysis plan. We've got time line here. We've got a patient who receives their first prescription for troglitazone. We define the baseline monitoring period as that time going from 30 days before to seven days after that first prescription.

We then looked at the monthly anniversary date from that index prescription for as long as the patient remained on troglitazone and looked plus or minus seven days from that date for evidence of reporting a billing claim for enzyme monitoring.

Next slide.

This gives an overall picture of the flow of patients in the study. Within the UHC database there are almost 9,400 patients who received troglitazone, contributing a total of nearly 4,900 person-years of time. Seventy-six hundred met the 90-day and prior enrollment screen, and 6,500 met the disenrollment or end of study interval screen.

So the data that I'm about to present now on enzyme monitoring is based on these 6,441 patients.

Next slide.

This slide summarizes the proportion of patients who started troglitazone in each of the time periods, the initial time period, the time period between the "Dear Doctor" letters, and the time period after the second "Dear Doctor" letter, the proportion who had baseline testing done, had a billing claim for baseline testing done within 30 days before to seven days after.

And what we see is that there has been an increase that corresponds to the "Dear Doctor" letters, but even in the final cohort, only 45 percent of patients had a baseline monitoring test.

Next slide.

This slide shows data on full compliance with monthly monitoring and baseline testing for troglitazone in this study, and to orient you, we've got each of the cohorts shown here, corresponding to the different rows, and then the number of months of treatment that a patient was experiencing.

And the way to read this slide, for example, is let's just take cohort three at three months. What this says is that in patients that start troglitazone in that last time period and were on the drug for three months and so were eligible to be

tested at that time, only 2.7 percent of those patients had a test done at three months, two months, one month, and a baseline.

At four months, it was less than one percent. At five months, it was zero, but we don't show the data there. At six months we had nobody in this last cohort who had opportunity to be on the drug for six months because our study period was only five months long.

To give the Committee a sense of study power, could we go to that previous slide for a minute, please, Lanh? Thank you.

To give the Committee a sense of the study power that we have here, we had 1,400 patients remember in that cohort who had a baseline test. This was 1,166 patients who were eligible; 9.3 percent of 1,166 had an enzyme test done. The denominator here was 636. Here it was 366. Here it was 182, and at five months we had 16 individuals, and as I said before, there were zero individuals out here.

So that gives you a sense of what we're talking about here. Okay.

Next slide.

The question comes us: what's the completeness of the data that we've used based on

claims lag?

Claims lag is you go and you have the test done, and then the place where you have the test done, they've got to process the claim with the payee, with United Health Care. So United Health Care collects data on how long does it take for claims to be processed and how complete are claims at different time periods.

In any event, based on those analyses, the claims data for cohort one are 99 percent complete, for cohort two 99 percent complete, and for cohort three they are better than 85 percent complete.

Next slide.

In this study we also looked at occurrence of clinical outcomes in patients, and we identified three patients who had codes that may signify acute liver failure, one with a code for transplant and two with codes for hepatic encephalopathy or acute necrosis.

Those last two patients, they processed no claims after that hospitalization. In other words, they are hospitalized with those diagnoses, and then they ceased to file claims. United Health Care says that that is a pattern that is seen in patients who die during that event.

We are in the process of obtaining medical records for those. So these are not validated at this time. We have only the claims data to base it on, but based on the claims data, these are the incidence rates for possible acute liver failure, for hospitalization with drug induced hepatitis, and for the combination of both from this study.

Next slide.

There are several other issues that I have to rush through before concluding. The question comes up, well, you know, there are other drugs on the market, and they cause liver toxicity. What are their risks.

The purpose of this slide is to give people kind of an overall sense in a general way of what we're talking about. We went to the United Network on Organ Sharing to obtain information on the drug association, the drug that was listed -- oh, here. Let me start again.

For patients who are registered for liver transplantation with UNOS because of acute liver failure due to a drug, what is the drug that was held responsible that it was attributed to, that liver failure? This information was obtained from UNOS through the Division of Transplantation in HRSA, and

so we thank them for it.

What we show is the drug group, the number who were registered for transplants. From IMS Health, we obtained the number of prescriptions for those drugs that were issued over the five-year period that these data encompass.

And then finally, we calculate a liver transportation registration rate per billion prescriptions with 95 percent confidence intervals, just more as a heuristic thing to sort of show people what we're talking about with troglitazone.

We've included sulfonylureas and metformin as other diabetes drugs. There were no registrations with liver transplantation for those. So we see what we have there.

With troglitazone, there were three in this time period, with 7.9 million prescriptions. So this is the liver transplantation registration rate and the confidence limits.

For nonsteroidal anti-inflammatory drugs, these are widely reported in the literature. There's a whole literature on NSAIDs and liver disease. The thing is, yes, NSAIDs do cause liver disease, but they cause it at a low rate. It can have a population impact because so many people take the drug.

So if we look there, in this five-year period there were six patients registered for transplantation and 372 million prescriptions, and so you've got a number of 16 for NSAIDs.

Now, Bromfenac-Duract is another NSAID, and it had two cases registered with 2.6 million prescriptions, and you can see the reporting rate there.

Finally, we include the statin drugs, the coase reductase inhibitors. They are reported to cause liver disease, but it's not generally severe liver disease, and we had one report in 206 million prescriptions, and you can see the rate.

So in this analysis, very qualitatively speaking, troglitazone looks very different than most other drugs.

Next slide.

Another question comes up. Metformin and lactic acidosis, the risk that it poses to diabetics, and so we have to be able to tolerate risks because it's a risk-benefit equation.

Well, the data we have on metformin and lactic acidosis comes primarily from studies based on reporting rates. It's not based on population based estimates.

However, there are two population based studies done in diabetics looking at the issue of lactic acidosis. One looked at patients studied who were taking metformin. The other was studying Type 2 diabetics who were not taking metformin. This latter study was performed by Kaiser Permanente Northwest in Oregon, but was funded by Bristol-Myers Squibb.

What we see here, however, is that the rate per million person years of observation for patients with metformin or Type 2 diabetics without metformin is identical. This is for lactic acidosis.

Furthermore, all of the cases that were identified in either of these two studies had recognized factors capable in and of themselves of causing lactic acidosis. So the question arises, you know, we talk about tolerable risk with metformin, but maybe what we should have been thinking about was, well, what's the risk in the study base, the base population, diabetics in general.

It may be that people who use troglitazone have the same risk of lactic acidosis as this group of patients, Type 2 diabetics, who don't use metformin. These are the only two studies that are available. There are not other population based data that we're aware of.

Next slide.

This summarizes the rates, the death rates per million person-years that seem to apply. For metformin/lactic acidosis we have a rate of 15 per million person-years. This comes right out of the FDA approved label, which says that the background rate is three per 100,000 per year, which would be 30 per million per year, but the death rate with lactic acidosis is about 50 percent. So we divided 30 by two, and that's where we get the 15, but the place where it comes from is the FDA approved label.

For sulfonylurea/hypoglycemia and death from that, we took the numbers from the sponsor's briefing package, 14 to 33 per million person-years, and then for troglitazone and acute liver failure, the estimates that we have are from population based studies.

Next slide.

I want to revisit under reporting once more before concluding. We presented before literature to suggest that reporting rates might be in the neighborhood of ten percent. Now that you've seen the data on the population based studies, we can do an observe to expected analysis using the rates seen in those studies to calculate what would be expected to

have happened in the entire U.S., compare it to what was reported, and come up with the reporting rate.

So from the DPP or REACH, UNC, we've got it all here. You can see for liver transplantation or death, the reporting rates, the reporting efficiency range from about two percent up to about nine percent. For hospitalization with hepatitis and troglitazone, the setting of troglitazone, somewhere between eight and ten percent.

We believe that these data provide internal corroboration of the literature that suggests that under reporting is substantial with troglitazone, and these data would lead us to believe that our estimate that we received only about ten percent of the cases is a fair assumption, and that the life table analysis adjusted for a reporting rate of ten percent is an accurate and fair portrayal of the data.

Next slide.

Okay. We've made it to the end, and if I have the Chairman's permission to go over my time by two or three minutes to complete these slides.

CHAIRMAN BONE: You recall that we were expecting to allow for the Committee members to ask questions in that time, but please wrap up.

DR. GRAHAM: Okay. Thank you.

CHAIRMAN BONE: Finish your remarks, but please be concise.

DR. GRAHAM: Thank you.

Okay. I want to make a few comments about benefit and risk and the way an epidemiologist looks at it from a population perspective.

We've seen today and we've heard today, this morning, that there's no question that individual patients have benefitted from the use of troglitazone. These benefits, however, have been in the short term, and in many of them they've related to things that relate to quality of life, and those are difficult things to quantitate.

We now have to sort of look at risk and benefits from a population perspective, and we have to realize that the major health benefits that we're talking about with diabetes therapy in general, troglitazone in particular, will be realized in the future, five, ten, 15 years down the line.

And I think it's important to focus on residual benefit, the residual benefit that troglitazone affords over other available treatments because that's really the appropriate benefit-risk decision to be made. It's not the total benefit of troglitazone necessarily, but it's its residual

benefit over other therapies if the Committee decides that those other therapies are safer than troglitazone.

The average troglitazone user is 61 years old. Well, what that means is competing mortality or lack of effectiveness of the drug will substantially reduce the pool of people who can stay on the drug long enough to realize these delayed benefits.

So what you have to think about is what's the present value of avoiding something that happens ten years or 15 years down the line.

Next slide.

The background rate for acute liver failure is about one per million per year, and for multiple population sources, we have estimates that suggest that it could be in the neighborhood of over 1,000 per million person-years.

The life table analysis, adjusting for under reporting, suggests a risk of 1,000 per million person-years at six months of use of the drug. That's very consistent with the data that we've presented here above.

The question is, from the other studies that we showed that were under powered, we really can't rule out a relative risk that may be as high as

3,000 or 6,000 per million person-years.

The hazard rate is elevated with the first month of use. It peaks at six months and then appears to remain high. We see no evidence that it declines. The cumulative risk progressively increases with continued exposure. So the question is: the longer you stay on the drug, what happens to that cumulative risk?

Most troglitazone users, while we have the under reporting and we think that we've only got maybe ten percent of the cases, the important thing for the Committee to realize is that most troglitazone users have not yet passed through the period of peak risk. So you have to consider that as well.

Last slide. There are no obvious predictors of who is at risk of developing acute liver failure with troglitazone. Acute liver failure appears to be unpredictable. The point of irreversible determinism seems to occur early in the process, and this is highlighted by the issue of rapid risers.

Enzyme monitoring occurs at a low level and in an irregular manner. We can't point to monitoring and say that this intervention has had any impact on the incidence of acute liver failure.

Finally, there are no data available on the efficacy of monitoring in the wave of preventing acute liver failure. That is, we don't know if monitoring can prevent this disorder in the first place.

That's the end of my presentation, and I thank the Committee for their attention.

Oh, final slide, just to acknowledge the people who helped us from United Health Care and FDA.

CHAIRMAN BONE: Thank you, Dr. Graham.

I'm sure there will be a number of questions about the content of your presentation. I think the plan will be for both the agency presentations and the presentations by the sponsor to ask specific questions that are related to the information presented, and then to reserve more extended discussion for the time designated for discussion. We did intend to include some question time, however, in the allotted time.

Are there questions from the Committee regarding Dr. Graham's presentation?

MR. HAMMES: Richard Hammes, University of Wisconsin.

CHAIRMAN BONE: Dr. Hammes.

MR. HAMMES: To get this in a little more

real perspective, is there any data in terms of the death rate of diabetics over age 45 in terms of deaths per million person-years?

DR. GRAHAM: Oh, I'm sure that data is available, and I haven't done the research on that, but what we're focusing on here is death due to a specific cause, not death due to heart attacks or stroke or the other things that diabetics deal with. We're focusing on the issue of hepatotoxicity with troglitazone, and in that context the appropriate thing to focus on is the rate of death or the rate of occurrence, the incidence of acute liver failure.

CHAIRMAN BONE: Was your question related to how to relate this to potential reduction in death from other etiologies or how did you intend that to be?

MR. HAMMES: Well, in looking through some of the written things here, there was one letter that came in that suggested that the risk of dying from diabetes was like one in 30. Well, you know, a risk from liver failure of one in 10,000 compared to the risk of dying in one in 30 has a whole lot different perspective than a risk of being struck by lightning.

DR. GRAHAM: Oh, yeah. Let me address that, please, Dr. Bone.

That risk of one in 30 of dying of diabetes is the background rate that all diabetics face regardless of the treatment they receive. What we're looking at is the incremental increase, the relative increase in risk of death. We're looking at a very specific cause, and it may be true that one in 30 diabetics die over some particular time period.

The fact is, however, that applies to all drugs. You sort of have to keep these things separate.

If you look at the relative risk estimate, what this says is if I had two diabetics or 2,000 diabetics in each group and I had one group that's being treated one way and one group that's being treated another way, they're all going to experience the same background mortality rate, this one in 30 or whatever it is, but then there will be a residual difference that's due to the drug, that's attributable to the treatment they receive, and that's what we're focusing on here: the attributable death rate that occurs with troglitazone from acute liver failure.

And so it's important not to confuse these two things because then you lose sight of what the role and the effect of the drug is, and that's what we're focusing on here.

CHAIRMAN BONE: Dr. Braunstein.

DR. BRAUNSTEIN: Well, there's a lot of data presented. Let's see if I understand this.

The risk for an individual patient who is taking the drug for one year with full reporting would be one in 1,000 for having liver failure or death; is that right?

DR. GRAHAM: Suing the full reporting slide, not the slide adjusted for under reporting, I think we had, if I recall, at eight months it was like one in 15,000.

DR. BRAUNSTEIN: Well, let's say we just captured everybody.

DR. GRAHAM: Okay. if we capture everybody, then we go to that under reporting slide. It would be in the neighborhood probably of one in 1,000. We only model it out to eight months because that's as far out as our life table permits us to go.

So if you take somebody, say, at six months, the example that I gave, where the cumulative risk would be one per 1,800 individuals who stayed on the drug for six months, person time-wise you have to divide that number by two because it's six months' of time for a person-year. So that would be one per 900 person-years.

If it turns out that the hazard rate does continue and there's an increase in cumulative risk, we did not model it for this Advisory Committee, but sort of the short answer is that the absolute risk to an individual patient would be greater than one in 1,800 patients. Whether it would be one in 1,500, one in 1,200, one in 1,000, I can't exactly tell you, but that's the notion of cumulative risk

CHAIRMAN BONE: All right. Dr. Seeff.

DR. SEEFF: Could I just get a clarification on the timing of the development of liver disease? You've shown some slides here about the time from jaundice to encephalopathy. You've told us, I think, that there are three manifestations of liver disease. One is jaundice. One is elevated enzymes, and one is symptoms.

Within each of those three categories, what does the timing from receipt of the drug to the development of each of these manifestations mean and a range?

DR. GRAHAM: From the receipt of?

DR. SEEFF: From the receipt of troglitazone, among those who develop an abnormality -- let's start with jaundice -- what was the mean time from receipt of troglitazone to the development of

jaundice? And I'd like to have it as a mean and a range, if possible.

DR. GRAHAM: Right. We don't have those data here. We have the database here so we could actually run those analyses and get the answers to those questions for you, in general.

But clinically, there are only a handful of patients with abnormal labs, first, and in those cases the abnormalities weren't necessarily particularly severe, and the patients with symptoms in most of those patients, the timing of the symptoms was only a matter of between a couple of days and a couple of weeks before jaundice occurred.

But we could do those analysis, but it's only a handful of cases. The bulk of the cases were jaundice.

DR. SEEFF: The primary manifestation is jaundice then?

DR. GRAHAM: Yeah, and the interval from symptoms to jaundice for those other patients is only a matter of days to at most a couple of weeks. It's a very short range.

DR. SEEFF: And see that in at least one instance the duration between, I guess, the development of jaundice and hepatic encephalopathy was

as short as four days.

DR. GRAHAM: Actually you can have patients who present with encephalopathy before jaundice. The very hyper acute cases can occur in such a fulminant fashion that patients don't have opportunity to develop jaundice before they become encephalopathic.

This is an interesting point, and I'm glad you raised this question because there were two cases that we had that presented with elevated ammonia levels and encephalopathy prior to the development of transaminase elevations, and I don't know if it suggests anything mechanistically, but these were patients who sort of metabolically were already in liver failure before apoptosis or whatever other process occurred began to occur.

CHAIRMAN BONE: There's some questions over here. Let's see. We'll just start with I think Dr. Hirsch had his hand up first.

DR. HIRSCH: Yeah, I just wanted to clarify one thing, if you can help me out. I'm a little confused about the fact that so few people have been taking troglitazone for more than six months. I assume this means that they're just starting to take it now.

DR. GRAHAM: Right.

DR. HIRSCH: Do we have any notion of the number of people who took it and stopped taking it for any reason?

DR. GRAHAM: From the data that we have available, we're not able to make any inference about what the reason was for stopping the drug, and the reason why you sort of have that slide that shows things coming down like that is, in part, patients who start it and stop it, but also it's because you have a constant infusion of new patients who start the drug.

DR. HIRSCH: So you don't know what the combo is.

DR. GRAHAM: That's correct.

DR. HIRSCH: How many are starting versus -- we don't have good data.

DR. GRAHAM: Well, we could. We didn't do that for this presentation, but we could show what the contribution was due to the influx of new patients.

DR. HIRSCH: It would b every interesting to know the number of people who took troglitazone and stopped taking it for all reasons.

DR. GRAHAM: Right.

DR. HIRSCH: And what that is. Obviously

that's a very important denominator in another calculation that I just want to point out to you.

I just want to make sure I'm correct in this. My mathematics here, as you were talking and going along, is something like one per 1,800 at six months in the whole population, with the ten percent reporting rate, and also your model is a linear model. In other words, it's two per 18, et cetera, et cetera.

So, you know, if Rezulin were something like insulin, a great drug in diabetics, you'll be taking it all the time. It isn't something ordinarily that you would stop. So it's not much of a calculation to show that at five years if your model is correct and if all the Type 2 diabetics in America were taking this, you'd have in excess of 50,000 cases of acute liver failure. That's not a hard calculation to do. Is that meaningful or is that a stupid calculation?

DR. GRAHAM: No. We didn't model the data beyond where they go. What we say is that based on the data we have, we're experiencing very high rates and accumulating risk.

DR. HIRSCH: So that is a possibility.

DR. GRAHAM: And that it is quite possible that that would happen, and we see no evidence to

suggest to us that that won't happen. I mean, you have uncertainty about what happens in the future, but based on what we see, we don't see anything to tell us that that won't happen

DR. HIRSCH: So that would be the major cause of liver failure kind of of all time if that were -- you know, 50,000 cases of acute liver failure would be rather remarkable, right?

CHAIRMAN BONE: Let's confine ourselves to specific questions, please.

I think Dr. Marcus had a question and we're coming right along.

DR. MARCUS: Yeah, I'd like to follow up on that one in 30 issue. Let us suppose the background -- there's another shoe that needs to drop on that -- the background mortality rate, let's say, per unit time is one in 30 for someone with diabetes, and if you're going to add to that an incremental mortality rate of, say, one in 600, then that's like adding another five percent to that one in 30, and so if you had a treatment which reduced mortality that one in 30 by as much as ten percent, then that favors the drug in terms of the overall effect in the population mortality.

But if the treatment effect is only five

percent, then is it fair to assume that any savings of mortality you're achieving due to the beneficial effects of the drug in general on diabetes are a wash, given the incremental mortality due to that additional five percent?

DR. GRAHAM: Right. Well, a couple of comments. One, I think, and I would urge the Committee not to confuse the background rate of death from diabetes with the issue of death from adverse reactions to the drug because the mortality rates for cardiovascular disease and everything else will dwarf just about anything that we're talking about here.

DR. MARCUS: But the drug could cause a ten percent reduction in that.

DR. GRAHAM: Well, it could.

DR. MARCUS: I'm not saying it does, but it conceivably could.

DR. GRAHAM: It could, and what you have to do, the way to do that analysis appropriately is not to be looking at the deaths from cardiovascular disease, but what you do is if you wanted to do it this way, you take a large cohort of troglitazone users, a large cohort of SU users, a large cohort of metformin users, a large cohort of insulin, whatever you want to do; a large cohort, and then you follow

them through time to see what happens. What is their mortality experience?

And you look and see where people drop out, you know, and what they die of, and then you can sort of see what the years of potential life lost are, and then you have to really focus in on cause specific mortality.

If 95 percent of your mortality is cardiovascular disease, you can look to see what is the incremental change in cardiovascular mortality, but then you also have to look at, well, what's your death rate from lactic acidosis, what's your death rate from liver failure. They have to be treated independently.

And when you do that and you look at these different drugs, I think you could take the major -- I mean, an appropriate thing might be to take the major mortality, the major adverse side effects of the different drugs and the mortality risks associated with them, hypoglycemia with SUs, lactic acidosis with metformin if you believe that it's different than the background rate for diabetics, the risk of desk from liver failure with troglitazone, and compare in comparable cohorts what the mortality experience would be, what the years of potential life lost would be in

those cohorts due to those adverse effects.

That's the appropriate way to look at this.

DR. MARCUS: We don't have that luxury.

DR. GRAHAM: No, we don't have that luxury, but you do have the rates. You have the rates.

CHAIRMAN BONE: Well, I think Dr. Marcus is commenting that that would be informative if we had a quantitative estimate of the beneficial effects.

DR. MARCUS: I guess I'm trying to model what the degree of benefit to the mortality would have to be to overcome the added increment, to overcome by a factor of ten or a factor of 100, to find out --

DR. GRAHAM: I think it would have to be substantial, but I'm not an expert in diabetes, but what I've read from diabetes and the experts that I've talked to in diabetes, nobody has yet made the claim that there are data that show that there's a convincing impact on mortality experience to the treatment of diabetes.

We do have other endpoints where there appears to be beneficial effects, and so if your outcome is mortality, I think unless you have the data, it's difficult to do that balancing.

CHAIRMAN BONE: We're going to probably hear a lot from our diabetologist to discuss that point during the discussion section. I'd like to keep our time right now on the specifics of Dr. Graham's presentation, and we'll come right around the table in the pattern we started with.

And I think Dr. Fleischer has a question.

DR. FLEISCHER: I wanted to know, given the relatively short duration in patients on the drug, how powerful do you think your linear model of increasing risk over time is? Because that's a really critical calculation.

DR. GRAHAM: Well, when you're lost at sea without a compass, you use whatever you have, and this is a compass that we have, and what I've tried to do is use multiple compasses.

We've got this model that's based on spontaneous case reports and the literature that's suggested under reporting, and it gave us one suggestion. We went to population based data and in multiple different places, you know, lightning struck, and the compass points in the same direction.

And then we go back and we look at what do those studies predict about what the under reporting rates might be for liver failure with troglitazone,

and, lo and behold, it comes back and kind of sort of internally validates the model.

So I've got these different compasses, and they're all kind of pointing the same place. Now, how good a compass is it? Well, I won't know until I get to the North Pole, and so I would submit that the information is informative and that it is predictive in a certain general sense, and certainly the clinical trials all do point to a high, a high relative risk and a high incidence rate, and certainly the experience through eight months, that one in 1,800 patients could experience acute liver failure on the drug, I think that that is probably not far off the mark.

DR. FLEISCHER: And that's at six months?

DR. GRAHAM: Right, and that experience, the majority of patients on troglitazone haven't reached that six-month point yet.

CHAIRMAN BONE: Let's see. Go ahead, Ms. --

MS. KILLION: Killion.

CHAIRMAN BONE: -- Killion. I'm sorry.

And then we'll come around in order, please, from now on.

MS. KILLION: I was looking at one of your

benefit-risk analyses where it says that there is no predictor of who's at risk, but when I was looking through some of the other materials, it seemed to me that you said 43 percent of troglitazone users are female, and yet when you look at the 43 cases of acute liver failure, 70 percent of them were female. Wouldn't that be an indicator of a higher risk to women for liver failure?

DR. GRAHAM: It may be. I'm reticent to put a statistical test to case reports, but the clinical impression is there, that women may be at higher risk. This is something that's seen with other hepatotoxins, that women are at higher risk. So it wouldn't be at all unexpected, I suppose, that that's the case here.

The fact is even though women have higher risk, it doesn't mean that men are without risk. What it might mean, we have a composite risk. Let's say the composite risk is 1,500 per million person-years. Well, what that means is the risk in women might be 2,000 or 2,200, and the risk in men might be 1,000 or 800. It's still elevated in men as well as in women, but women are subject to a higher level of risk.

CHAIRMAN BONE: Thank you.

Let's see. Dr. Colley, did you have a

question? No or yes?

DR. COLLEY: I was impressed by the abysmal adherence to recommended monitoring that you found, and my question is are you able to determine if monitoring in the most recent labeling had been adhered to, would you be able to detect those cases?

DR. GRAHAM: If monitoring had been done, sort of like we're agreeing that it hasn't been done, but had it been done could we have detected what, people who would have abnormal liver enzymes? Could we have prevented liver failure? Is that the question?

MS. KILLION: Yes.

DR. GRAHAM: Well, that is what I was trying to get at with the rapid riser issue, and the problem is we only had 12 cases out of the 43 where we sort of know the time course, where we've got liver enzyme measurements close enough to when liver failure was diagnosed, when they had reached that irreversible place, to sort of know what the time course was.

For nine of those people what we found was that they went from a normal enzyme to irreversibility in like basically one month, one monitoring interval. For the other three, they had enzyme abnormalities that were seen to increase, you know, sort of from one

month to a next month and then to irreversibility.

So we have an N of 12, and nine of them, you know, 75 percent, the answer to your question would be would fail in a monthly monitoring system to prevent that, and then the question is: for everybody else that we don't know, well, what happens to them?

And so we looked at the clinical content and saw no distinguishable characteristics that would allow us to distinguish who a rapid riser is from any of those people, leading us to wonder, you know, are most of them rapid risers as well.

CHAIRMAN BONE: Thank you.

Dr. Cara, you had a question?

DR. CARA: Yeah, I have a question that will hopefully help me separate out a little bit the apples and oranges that we're getting in all this information, and it primarily relates to the sort of numerators and denominators that you versus the sponsor are using.

They've limited their comments about hepatic failure and risk of hepatic failure primarily to their studies. However, when you estimated the risk of acute liver failure with troglitazone it was more of a, quote, unquote, real world sort of situation where you took patterns of troglitazone use

from the UHC database.

My question is: was that database specifically evaluated in terms of diagnosis? In other words, did you essentially take all troglitazone prescriptions? Were these specifically for people with diabetes?

DR. GRAHAM: We took anybody who was treated with troglitazone.

DR. CARA: Regardless of the diagnosis?

DR. GRAHAM: Well, you can't -- unless you go back to the medical records, you won't be sure of the diagnosis, and based on the age of the patients, we had very few patients who were under the age of 45 who started the drug, and so --

DR. CARA: Well --

DR. GRAHAM: Well, our presumption is that most of them are Type 2 diabetics.

DR. CARA: Well, but that may not be an adequate presumption because troglitazone is being used more for other sorts of conditions, including --

DR. GRAHAM: Well, then here's another statistic then that maybe will help nail this down. Only 12 percent of the entire UHC population was on troglitazone monotherapy. All other patients, so 88 percent of the patients, were on other drugs used to

treat diabetes. Most of them were on sulfonylureas, metformin and insulin.

I have a slide. We had it in the original slide show. It got cut. You saw we went a little over time. That slide would have taken ten minutes for people on this Committee to understand because of its complexity. I think it may have been in the original package that went out. I don't recall.

But in any event, these data would lead us to believe that the overwhelming majority of troglitazone is used to treat Type 2 diabetics, I mean.

CHAIRMAN BONE: Thank you.

Let's see. Let's just so over there. Go ahead.

DR. KREISBERG: Okay. Dr. Graham, I'd like to address two issues with you, and, Henry, I'd like to be able to come back to Dr. Graham after the sponsor has a chance to make a presentation because I think that --

CHAIRMAN BONE: Well, let's see how the program can go.

DR. KREISBERG: Okay. The first issue is, and I'm addressing now a slide that shows up on page

17 of the handout, which is called "Summary of Population Based Data on Risk of Acute Liver Failure with Troglitazone," in which you do modeling, and based upon two actual cases, you come up with specific recommended rates that range in the range of 1,200 to 1,700 per million patient-years with very wide confidence intervals.

But I'm impressed that you even come up with confidence intervals where there are no cases of liver toxicity.

DR. GRAHAM: No, no. That's binomial. I mean, that --

DR. KREISBERG: Well, you're way over my head, but it just intuitively doesn't make much sense to me.

DR. GRAHAM: No, what that confidence limit tells you on a study with no outcomes is it speaks back to the power of the study to rule out a certain level of risk, and what we're saying here is that these studies are basically uninformative as to what the point estimate is.

They are informative, however, in telling us what the rule out level is and what one could do if thinking sort of in risk-benefit. I'll give you an example.

DR. KREISBERG: You don't have to do that. I understand what you've said.

DR. GRAHAM: No, no. This is an important example to understand risk-benefit and the use of confidence limits.

In designing studies for safety one goes to design them to rule out an upper level of risk, that one is comfortable still permits a favorable benefit-risk analysis, and so these give us information on that, on what the upper bound might be. These studies don't exclude those risks, and so the Committee could use that information in its formulation of benefit-risks to say are we comfortable with the risks being at this particular level, at that upper 95 percent bound.

DR. KREISBERG: In this slide you have two documented cases of acute liver failure in five studies that you reviewed, and on the basis of those two cases, you make an estimate. Now, what I want to ask you about this particular slide is how do you know that this is not a Type 2 error, and that is, how do you know you're assuming that a difference exists when one actually doesn't exist based upon the infrequency of the events?

DR. GRAHAM: It has to do with the

background rates, that one in a million background rate, and if I had put P values on these studies, you'd see P values that are like ten to the minus six. I mean we're talking about P values that are just unheard of.

And to have it happen in two different studies, it's sort of the same way when you guys go and review two different clinical trials to say that the drug is effective, and you require that both of those trials be a .05 level.

And the reason for having two studies is because your probability of making a Type 2 error with two positive studies is like basically .05 times .05.

You've got two studies here where lightning struck, and the question is: what's the probability of a ten to the minus 12 event happening and not being real?

And then you do the modeling as well and all of the other evidence about under reporting, and it comes up with the same exact answer. So the fact that you've got zeros in these under powered sponsor studies is a fact that relates perfectly to their being under powered.

If I had had 20,000 patients on troglitazone for one month and I found nothing because

those patients hadn't gotten to the period of high risk, or 20,000 patients on the drug for one week or one day, and it gives you a certain number of people and you don't see the events, it's not told you very much about what the actual risk is because it doesn't have the ability to find it.

DR. KREISBERG: Can I ask my other question as well?

DR. GRAHAM: Go ahead and finish.

DR. KREISBERG: Okay. The other issue has to do with what you said and the estimate that Dr. Hirsch made about 50,000 cases of acute hepatic failure, and that sounds to me as if you're saying that this is not an idiosyncratic reaction because over time, you expect to see a cumulative increase, and that suggests that time will bring it out.

What's the possibility that time will bring out the reaction in those individuals who are susceptible to it, but not in those individuals that are not?

DR. GRAHAM: That's perfectly possible. What you're doing then might amount to sort of almost a eugenic sort of selection process though because what you're really doing then is let's propose, for example, that it's due to an underlying metabolic

polymorphism, and we're selecting out people who are sensitive.

Well, we have to identify what that polymorphism is and the mechanism and everything else to select those patients out so that they don't get exposed to the drug, and if you were able to do that, then maybe if that were the mechanism, then maybe you could eliminate acute liver failure from happening.

The fact is we don't know what the mechanism is. All we can do is say what we observe in the rates, and what we observe in the rates is that as far out as eight months we have not weeded the population of everybody who's susceptible to acute liver failure from troglitazone. They're still there.

DR. KREISBERG: Thank you.

CHAIRMAN BONE: Dr. New.

DR. CARA: Just can I just make a follow-up comment?

You're assuming that the population that is on troglitazone is constant.

DR. GRAHAM: Well, no. What I'm assuming is based on the data that we have up to now, is that you'll continue to have new people who get on board who start at month one and then have to ride basically the train through six months and then out beyond. so

they've got to ride the trade from a period of background rate, when they're not on troglitazone of, you know, one per million per year, hop on the train in the first month, have a rate of 56 or whatever it is with under reporting, and then take the train up the hill to 185 or whatever it is, and then follow at that high altitude until I don't know how long.

And so somebody who starts the drug today, these are sort of the mortality risks that that patient will have to pass through as they go through time.

CHAIRMAN BONE: Okay. Thank you.

Dr. New.

DR. NEW: Dr. Graham, did you control for the possibility that at the moment that there is a rapid rise or a sudden fatal hepatotoxicity that induces death, as you've just said, in the absence even of liver function abnormalities, that this could be due to the fact that somebody was taking another medication?

DR. GRAHAM: In virtually all of the cases, other medications were excluded. About 20 percent of these patients were taking concomitant statins for hypercholesterolemia, which is the exact percentage found in the United Health Care database.

Acetaminophen wasn't implicated in any of the cases, and there was not a common thread in any of the cases.

In terms of those two case, it's not that they didn't have liver enzyme abnormalities. It's that the ammonia elevations preceded by a couple of days the development of high transaminase levels.

DR. NEW: Dr. Bone, I just want to refer back to Dr. Marcus' question about putting the risk of troglitazone on the background of the risk of diabetes, and I think we have to come to that because I don't think patients care whether they die of troglitazone poisoning or of diabetes.

DR. GRAHAM: Well, could I make one comment on that, which is --

CHAIRMAN BONE: We're going to have our discussion later. We're going to concentrate on specific questions about Dr. Graham's presentation. We've already spent quite a lot of time trying to get at that as pieces of information. I think we should focus on that for the rest of this time period.

Dr. Molitch.

DR. MOLITCH: I have a couple of questions that deal with the interval specific hazard rate and then the cumulative risk, and perhaps my naivety as a

statistician, and in addition, I have a question about the nature of the under reporting of acute liver failure and your estimate that it's only ten percent.

But I understand that you made a number of other efforts talking to transplant centers, UNOS registries, et cetera, to ascertain these 43 cases of acute liver failure. Do you really think, in fact, over this time period that there are 400 cases of liver failure occurring in this country and not 43 or do you feel that that 43 is actually a fairly close representation of the true number of case?

DR. GRAHAM: No, I think that the number is closer to 400 than it is to 43, and that most cases with acute liver failure don't make it to transplant centers, and that most patients with acute liver failure due to drug induced cause don't receive transplantation for it.

I mean we'll leave -- the University of Texas has -- I don't know where he gets the data from, but it's in two of his publications that only one in ten patients with acute liver failure get transplanted. So I do believe that the number of cases of acute liver failure with troglitazone is much closer to 400, and the internal consistency of the data would suggest that it's about ten times as much

as the number of cases we have reported.

DR. MOLITCH: But the internal consistency of the data, again, deals with one case in a couple of large series that come up with that same kind of figure.

DR. GRAHAM: Well, now, you've got the DPP. You've got the REACH study, and although it's not validated, we have from the United Health Care what appears to be data that are consistent with the other two, and then we have the modeling that we did that ends up giving us a predicted rate, that 1,000 per million person-years at six months that's virtually on the nose with everything else, coming at it from an entirely different angle.

And so it's sort of like different threads of information coming from different sources that are unrelated, giving rise to very similar estimates of risk are what we find sort of persuasive, or at least I find it persuasive.

DR. MOLITCH: I just find a very thin thread, and with all of the media hype that has gone on over the last year, I wonder whether, in fact, it's still just a ten percent under reporting.

DR. GRAHAM: Well, what we know about stimulation of reporting, we don't see the evidence of

it in the cases. I mean, you know, it's always possible that some cases are stimulated, but you still have, you know -- if it turns out that we've got, you know, 12 percent of the cases instead of ten percent or 15 percent instead of ten percent, we don't have 25 percent. I mean that's an unheard of reporting rate in the United States.

DR. MOLITCH: My second question deals with the interval specific hazard vapors as cumulative risk, and it looks like the intervals specific hazard rate does go down after six months; is that correct?

DR. GRAHAM: Well, what happens though is that the confidence bounds go up. So the point estimate has gown down. It's still above what it was in the preceding months, and in the last month, it flips up to a level that's intermediate, but the confidence limits on that are such that who's to say that it does in truth. We'll only know with the accumulation of additional cases.

DR. MOLITCH: But to take that to a specific patient situation where we have a patient in the office that we're treating, if we are seeing a patient who has had normal liver enzymes for six or eight months, is that person still at the same increased risk at month nine, is what you're say, than

what they were at month four?

DR. GRAHAM: Yes, yes. Clearly, at month four whether they're at the same risk as month six, I would feel less comfortable about saying that it's exactly the same. I would say that qualitatively it's the same. It is still far above what the background rate would be.

DR. MOLITCH: Was this information known when you came up with the eight month recommendation for the liver function testing?

DR. GRAHAM: Oh, no, no. I mean, I think that eight months -- well, Dr. Bilstad and Dr. Sobel could talk about how that number was come up with.

These analyses were not done until preparation for this Committee.

CHAIRMAN BONE: Thank you.

I think Dr. Temple had a question for Dr. Graham.

DR. TEMPLE: Yeah, I do. Just one point on the last discussion. Many times people think that the so-called idiosyncratic liver reactions are things that only occur early. So the crucial question isn't so much whether you can pin down the exact rate as to whether the risk is essentially gone after a period of time, and I think David would argue he can't pin the

numbers down, but he's saying it looks like it's not gone. You continue to get late cases.

I had a question about page 17 also. You explained why you decided not to pool the various population based data, but by doing that, in a certain sense you give the studies that didn't have any cases no credit at all.

So my question to you is whether you did, even though you don't think it's the right thing to do, do an overview of those studies and come up with a rate.

CHAIRMAN BONE: Excuse me. For the Committee, where is this?

DR. TEMPLE: Oh, I'm sorry. It's page 17 of the handout.

CHAIRMAN BONE: Which handout? There are several.

DR. TEMPLE: David's slides. It was already referred to once. It's called "Summary of Population Based Data on Risk of Acute Liver Failure."

PARTICIPANT: The material we received, page 17 has something else.

DR. TEMPLE: NO, no. I think it's a handout that just came around. It's his slides.

CHAIRMAN BONE: Oh, this handout. All

right. Not the briefing book.

DR. TEMPLE: No.

CHAIRMAN BONE: I'm sorry. Please go ahead.

DR. TEMPLE: Okay. It's a list of five studies. It's the one that people have been discussing.

CHAIRMAN BONE: Yes.

DR. TEMPLE: It shows two cases among five studies. Three studies don't show any, and you have confidence limits for them, but what you don't get is what might be called an overview of those data, which you can guarantee will give a somewhat lower rate.

DR. GRAHAM: Well, now a couple -- okay. Thank you, Lanh.

DR. TEMPLE: let me just finish my question. I did it crudely. I get a rate of about 500 per million, which you know, is close enough to 1,500 so that it may not matte.

DR. GRAHAM: Right.

DR. TEMPLE: But it is different.

DR. GRAHAM: Okay. Well, a couple of things that I'd say about that, Dr. Temple. One is that there are a number of other studies that aren't shown on this slide. We can only fit so many on a

slide, but they were in the sponsor's briefing document.

If you were to contemplate grouping these studies together in some sort of meta analytic way, I would say that it's absolutely necessary to create strata that cover different time periods on drug because of the way the hazard changes over time, and that when you do that, it's a shame. This is a slide that was in the talk, but it was another one that had to get pulled out because it's too complicated.

If Dr. Bob O'Neill were here in the audience, he could discuss it because it was from an article that he wrote, but what it basically says is that you've got to take the patients who are on the drug, say, from zero to three months, and then for more than three months up to six months, then eight months, and take those different strata and the proportions in each study, and then basically do a Mandell-Henzel analysis that looks at the power within each of those strata to identify the risk.

Now, in the talk, I gave a discussion about that I did that for the NDA study, and what I found is that the grouped analysis gives you this upper bound of 2,500, but if I looked at the place where the risk is really greatest, in this group over

six months, that the upper bound was actually 5,600 or close to 6,000.

And so it actually works opposite. You get the smaller confidence limit, but it's because you're grouping all this time, this two months and one month in the Sankyo study and this Galaxo study and all those other studies, and so you're diluting the effect.

So if you were going to do a meta analysis and you were going to combine these data, you'd have to stratify for time.

DR. TEMPLE: I guess I'd say that depends on what you believe most about which the data are.

CHAIRMAN BONE: Okay. Thank you.

We're going to come around, and we have other members and we'll come around. Let's see. Dr. Lewis.

We can leave this slide up for the moment if you'd like or just have it read to retrieve.

DR. LEWIS: I'd like to come back to the issue of exactly when the cases are occurring among these 43 that we know about. If we look at page 8, the slide on that that talks about the characteristics of the 43 patients, the duration of therapy is a fairly -- it's short at four days and it's up to 236

days. How many of the patients were actually within the first month --

DR. GRAHAM: Of the cases?

DR. LEWIS: -- of the case.

DR. GRAHAM: Right.

DR. LEWIS: Where they were only taking troglitazone for 30 days and the event occurred.

DR. GRAHAM: Right. I think it's unfortunate. That was another slide we had in our talk, and it got censors. I'm just saying this to let Dr. Ho know.

CHAIRMAN BONE: We're really short on time, and we don't need that discussion. Let's go.

DR. GRAHAM: I think the answer was five.

DR. LEWIS: So only about ten percent were in the first month. So most of these occurred within the subsequent few months, and it doesn't seem like there was anybody after eight months of treatment.

DR. GRAHAM: But we have no reported cases of liver failure after eight months. The problem is that the denominator of use of patients who are at risk to develop it is down there below 30 percent of the population, and so what that means is that in order to sort of produce cases that get through the under reporting and everything else, you really have

got to wait for time to accumulate there, and then we'll be able to test the hypothesis fairly.

CHAIRMAN BONE: All right. Dr. Illingworth, did you have a question?

DR. ILLINGWORTH: From your analysis of the results, is it possible to estimate how many patients were on other drugs or were taking other drugs briefly that are metabolized by the cytochrome P3A4 system?

DR. GRAHAM: Okay.

DR. ILLINGWORTH: And may be potentiators of inducing toxicity under stable conditions?

DR. GRAHAM: Right. The majority of patients, the drugs that they -- were basically only on drugs for the treatment of their diabetes. About 20 percent were on statins, and then there were two or three patients who were on various NSAIDs, and there were a few patients on calcium channel blockers, but the majority of patients were on those drugs.

DR. ILLINGWORTH: I'm thinking specifically of a patient, say, that had been given erythromycin for an acute infection. Could that have been the trigger in some case or was that looked at?

DR. GRAHAM: Yeah. In no patient was there a setting like that. Patients, you know,

started the troglitazone. If they were on other treatments, most of the time those treatments had been continuous, and the troglitazone was added to it, and there was no like particular drug that stood out as a common thread in, you know, more than a few cases at a time.

CHAIRMAN BONE: I think Dr. Genuth is next.

DR. GENUTH: Could you put up the slide again, the infamous page 17 slide?

When I looked at that slide, like Dr. Kriegsberg, I was intuitively puzzled. So I'd like to ask his question just a little differently.

You want us to focus on the 95 percent confidence intervals and, in particular, the upper for safety purpose.

DR. GRAHAM: Right.

DR. GENUTH: So I'd like to know in your calculation, in a study where there are no events or even a study with one event, how reliable is your estimate of the upper 95 percent confidence interval?

DR. GRAHAM: Well, it has the statistical properties of a 95 percent upper bound, and what a 95 percent upper bound says is that we can be 95 percent sure, and if you do it one sided and you make it 90

percent bound, we just say that there is a five percent chance that the rate that we're observing could be greater than that.

DR. GENUTH: No, I understood that. I want to know how reliable the 95 percent confidence intervals are when there are zero events or one event.

DR. GRAHAM: Well, no. I'm not a statistician either, but you use programs like SAS where they've worked out the statistics of it, and it's statistically accurate.

What level of, say, imprecision there is is expressed in the width of the confidence interval. That's sort of the best answer I can give.

DR. GENUTH: I know we're short of time. Let me try to get at it slightly differently.

DR. GRAHAM: Okay.

DR. GENUTH: When you calculate a 95 percent confidence interval in a study where there are ten events versus a study where there are zero events --

DR. GRAHAM: Right.

DR. GENUTH: -- is there a difference in the confidence you can have as to what that upper bound is?

DR. GRAHAM: No. Well, what you know is

that the bound -- when you have more events in a given study, your upper bound will come in closer. So part of the problem of what we're dealing with here though is that you're dealing with an event that has a background rate that's just so incredibly low that in order to bring that bound down to, say, closer to the point estimate if the point estimate is 1,000 or it's 1,200, to bring that upper bound down to 1,500 or 1,800, the size of a study that you'd need to do that, I mean, dwarfs the imagination, I mean, because you're dealing with a background expected rate of one in a million.

And so you're sort of trapped in this dilemma, but what we're pointing in that upper bound risk is basically the incidence rate. What is the upper possible incidence rate from these data?

CHAIRMAN BONE: Let's see. Dr. Braunstein, did you have another question or comment?

Do I understand correctly then that the number of cases of idiopathic acute liver failure in the United States is about 200 per year?

DR. GRAHAM: That's correct.

CHAIRMAN BONE: Have we seen a tripling of the number of cases of idiopathic acute liver failure?

DR. GRAHAM: They don't collect statistics

on that. So you have to sort of -- you can look at transplants, but most patients don't make it to the transplant centers.

There's no central place where this data is all collected that you could sort of look for for secular trends. One might be able to -- I mean even death certificate data is incredibly difficult to use. So there's not an easy answer to look to see has there been a secular effect.

CHAIRMAN BONE: Yeah, and how many transplants are done a year?

DR. GRAHAM: It's about 4,000, 4,500, and as I showed you before, about six percent, it turns out, are done for acute liver failure, and of that six percent a smaller percentage, you know, less than, you know, a quarter are due to transplantation for drug induced causes.

CHAIRMAN BONE: Well, let me see then. That would mean that you would have how many done per year for drug induced causes? A quarter of --

DR. GRAHAM: Well, I mean, it's really hard to answer these questions without having -- we have a lot of these slides in sort of like background material.

CHAIRMAN BONE: Just please do the

arithmetic. You said about 4,000 liver transplants.

DR. GRAHAM: Right, and about six percent. Six percent of 4,000 would work out to like 240.

CHAIRMAN BONE: Two hundred forty, and a quarter of those would be 60.

DR. GRAHAM: Well, it's less than a quarter. There's a slide, Lanh, that was the UNO slide on transplants, and it was like .66 per million and .11. So about a sixth of transplants for acute liver failure are due to drug induced causes. That's like about 15 percent.

CHAIRMAN BONE: And you don't think that that 40 or so -- that's about 40 a year. So you think that --

DR. GRAHAM: Yeah, 40 or 50.

CHAIRMAN BONE: -- if we had ten percent of the people going to transplant, that would double the number, but you don't think you'd have picked that up in your --

DR. GRAHAM: Oh, not in the -- the data that we have don't go through the period of time, and actually we know from our data of like about four or five patients with hepatitis who were placed on a transplant list, and then we have the seven patients that we know were transplanted, and all of these

occurred before December '99, but they're not reflected yet in the UNOS data.

So I can't explain what the lag is there on their end.

CHAIRMAN BONE: All right. You can see where I was trying to get a little corroboration.

DR. GRAHAM: Right.

CHAIRMAN BONE: I think one of the concerns that many of us would have had to do with the estimate of the under reporting and the validation. I had a little trouble following the relationship that you have found between your estimate and the number of cases that you had from the HMO data.

DR. GRAHAM: Can I explain that?

CHAIRMAN BONE: Yes, concisely, please.

DR. GRAHAM: Okay. Take a study. Let's take the DPP study or the REACH study. Take the REACH study, and in the REACH study we had a rate of like what, about 1,200 per million person-years for liver failure. Well --

CHAIRMAN BONE: That's with confidence limits of 32 to --

DR. GRAHAM: Right.

CHAIRMAN BONE: -- 7,000 for those who don't have the slides.

DR. GRAHAM: Right, and I based the under reporting rate on the point estimate, which I think is a reasonable thing to do, and what you do is you say: well, okay, in the United States what's the cumulative person-year time of exposure to troglitazone?

The answer is about 676,000 person-years of time, all troglitazone use from March up through December '98.

Okay. Divide that number, 676,000, by the number 1,274, and that will give you the number of expected cases, and then compare that number with the number that's reported, and that's your reporting rate, and that's called an observe to expected analysis, and I had slides to talk people through this one, too.

CHAIRMAN BONE: Excuse me, Dr. Graham. You've made that point several times. The point is here though --

DR. GRAHAM: Well, no, but it would help if you could see it to focus on.

CHAIRMAN BONE: But it also appears to me that if you -- but when you're making that estimate, it has extremely wide confidence limits on that estimated occurrence rate.

DR. GRAHAM: Well, we can recalculate it

going with the lower bound and recalculate it with the upper bound. In the end, you're kind of left with, you know, having to make a decision, and the point estimate to me just seemed to be the fairest place because the point estimate is what was observed.

CHAIRMAN BONE: Well, yeah, that's one case, and that's the point that's been made here.

DR. GRAHAM: Well, but it's a very rare event and --

CHAIRMAN BONE: Let's don't have a debate about this.

The other question I specifically had though was relating your occurrence rate in cases of acute liver failure or hepatitis and the HMO group that you had. You had three cases of acute liver failure, I think, and four --

DR. GRAHAM: Yeah, that's claimed, and four of hepatitis, hospitalized --

CHAIRMAN BONE: And those cases have not been investigated?

DR. GRAHAM: We have not obtained the medical records yet. That's correct.

CHAIRMAN BONE: Okay. Now, did you use those estimates from that database? I thought I understood you to say that you attempted to relate

that to this reporting rate question, and that's what I was trying to get at here.

DR. GRAHAM: No. In a slide right before my summing up slides, I took the study, the DPP study, the REACH study, the UHC study, and the NDA study and calculated what the reporting rates would be using those rates just to give people a full flavor. You could cross out the UHC line if you wanted to cross it out.

CHAIRMAN BONE: No, I was just trying to understand.

DR. GRAHAM: But the fact is that actually the UHC line gives you a higher reporting rate than with the other studies.

CHAIRMAN BONE: Well, with unadjudicated cases.

DR. GRAHAM: Well, there we had three, but they're not validated yet.

CHAIRMAN BONE: That's right. I mean, we don't know whether they had viral hepatitis or something, too.

DR. GRAHAM: Well --

CHAIRMAN BONE: We can't use those cases.

DR. GRAHAM: -- we don't know it exclusively, but the codes that we have don't indicate

that, and usually --

CHAIRMAN BONE: That's what I was -- I was trying to get at how you'd use those cases without having reviewed the records.

DR. GRAHAM: But I think we presented it in the context of all the other data that are available.

CHAIRMAN BONE: I understood that part.

DR. GRAHAM: Okay.

CHAIRMAN BONE: Thank you.

Dr. Lewis or anyone else? We have final questions here.

It's now noon. So we're going to have to make some plans about how we're going to proceed after this discussion, but go ahead.

DR. LEWIS: Just in terms of these severe adverse drug reactions and the under reporting, is it the same for fatal adverse reactions as it is for headaches or diarrhea?

DR. GRAHAM: No. For hospitalization or death, the reporting rates seem to be very similar. For less severe adverse reactions, the belief is, and in places where it's been looked at, those reporting rates are even poorer than for the severe reactions.

DR. LEWIS: Right, because as a practical

matter, we're not seeing this epidemic of fulminant hepatitis due to drug or other things. I mean it's been a fairly constant rate. There are several hundred cases a year of viral hepatitis that are fatal and a number of drugs, some of which are known to be the drugs and some are not.

And the question about how many people get transplanted for acute drug induced liver disease that's failed, it doesn't mean that they all don't get the transplant centers. More and more people are actually being evaluated, but they don't necessarily get transplanted because of co-morbid disease. They may simply be too sick when they get there, and we don't have really good numbers on that.

DR. GRAHAM: Right.

DR. LEWIS: But, you know, whether it's 43 cases or whether it's really been 430 cases, it doesn't sound like it would be the 430 from what you just said when we do have better reporting of the more severe toxicity.

DR. GRAHAM: Well, one thing to say about that has to do with attribution of the liver failure to a drug, and in several studies where that's been looked at even, say, for fatal INH hepatitis, the attribution gets made in only about a quarter of the

cases, and so you run into this problem that when you look at acute liver failure and the way it's classified by transplant centers and you have this category that's called drug induced, and then you've got this category that's called "unspecified," which is basically they haven't made the attribution, and we have examples of cases here where patients presented and the attribution wasn't made initially because it just didn't click.

So you have that problem to deal with as well.

DR. LEWIS: That runs about 25 percent.

CHAIRMAN BONE: All right. Let's see. Wrap-up questions as far as Dr. Graham's presentation? Dr. Genuth.

DR. GENUTH: I realize you don't have this data now, but in your collaboration with United Health Care, is it possible for you to learn what proportion of patients who start Rezulin stop it for lack of efficacy?

DR. GRAHAM: I'd have to think --

DR. GENUTH: In the doctor's mind or patient's mind.

DR. GRAHAM: Right. Such a study could possibly be designed, but what it would involve is our

having to go back to the physicians to understand what was going on, and that would be a more complicated and expensive study, and it wouldn't be the focus of what our cooperative agreement is intended to do, which is to study the adverse effects rather than something like this.

So it theoretically could be done, but it would be a difficult study for us to do.

CHAIRMAN BONE: Thank you.

Thank you, Dr. Graham.

This is a final question, Dr. Cara, about Dr. Graham's presentation.

DR. CARA: I'm concerned about the fact that when you look at the date from the sponsor, again, there is about half of their cases of acute liver failure were patients on monotherapy, whereas in your population based data you said that about 80-plus.

DR. GRAHAM: I don't think 50 percent of the cases were on monotherapy with troglitazone.

DR. CARA: Twenty out of the 43?

DR. GRAHAM: No, I don't think that that's correct.

CHAIRMAN BONE: Maybe we can clarify that during the lunch hour and have actual facts instead of

standing --

DR. GRAHAM: Right. We can check our database.

DR. CARA: Thank you.

CHAIRMAN BONE: It's now 12:06 by the Chairman's standard time.

(Laughter.)

CHAIRMAN BONE: The sponsor has agreed to give their presentation straight through following the lunch recess, which will be for -- we are really going to start at 12:45. So that's going to compress the lunch slightly.

Please be here in your seats ready to go at 12:45. We've got to get back on track.

(Whereupon, at 12:06 p.m., the meeting was recessed for lunch, to reconvene at 12:45 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(12:46 p.m.)

CHAIRMAN BONE: The first presentation of the afternoon will be the introduction by Dr. Robert Zerbe of the sponsor, and then there will be a series of presentation as you see in the program.

We are going to go straight through the sponsor's presentations since we have already taken the lunch recess. Committee members have been asked to reserve their questions until the end of the presentation.

Please be quiet in the back, please. The Committee is in session, and we're proceeding now. Thank you.

The company has advised me that they anticipate that questions that may arise during some of the earlier presentations will be answered as they go along with the subsequent ones, and in the interest of efficiency and flow, have asked that we reserve questions until after their presentation.

We'll then have a period specifically directed to questions about the presentations by the sponsor's speakers, and then we'll have a general discussion. So we'll try to stay on task on those two separate areas.

Thank you.

Dr. Zerbe.

DR. ZERBE: Yes. Dr. Bone, Advisory Committee members, and guests, I'm Dr. Robert Zerbe, Senior Vice President for Clinical Research and Development at Parke-Davis, and it's my pleasure to introduce our presentation on the risk-benefit assessment of Rezulin, a novel treatment for Type 2 diabetes.

We appreciate the opportunity to share this valuable information in a scientific forum, and we look forward to your comments.

It was a little over two years ago when we presented for the review of this Committee the initial clinical efficacy and safety data for Rezulin. The review at that time was based on an NDA submission filed in July 1996 which showed significant improve in glycemic control when Rezulin was added to insulin in patients who were inadequately controlled with insulin alone.

Following a positive recommendation by the Committee, the FDA granted approval of the initial application in January 1997.

An SNDA submission to extend the indications to include both sulfonylurea combination

and monotherapy was submitted in February 1997 and was approved in August 1997.

In November 1998, another SNDA was filed to extend the indications to include the addition of Rezulin to patients who had failed the combination of sulfonylureas and metformin. This efficacy supplement will be discussed today.

Rezulin has shown excellent efficacy as demonstrated by significant reductions in hemoglobin A1c whether it is added to a treatment regimen of patients who have failed diet, failed sulfonylurea, failed insulin, or failed the combination of sulfonylurea and metformin. Clinically significant reductions in hemoglobin A1c resulted.

In the groups which continued previous therapy, the hemoglobin A1c either remained the same or increased, as indicated by the white bars. These clinically significant effects will be discussed extensively later in the presentation.

Clearly, Rezulin is quite effective when administered in a variety of situations, and this efficacy has translated into wide use of the drug since its launch approximately two years ago. Since that time over 1.5 million patients have been treated with the drug.

Now, over that time, there have also been significant label changes related to safety. Dr. Bilstad reviewed these in detail. So for the sake of time, we will not repeat them.

Sine the initial observation of severe hepatic failure, Parke-Davis has worked closely with the FDA and outside consultants to better understand the mechanism and epidemiology of these events. We have tried to better define populations that can gain the greatest benefit and, perhaps most importantly, professional educational initiatives were undertaken to inform physicians and patients about the importance of monitoring.

Fortunately, these efforts have reduced the occurrence of severe liver events. The data shown here, which will be presented much more extensively later in the presentation, demonstrate that the reports of jaundice have been decreasing since this series of label changes were initiated by Parke-Davis.

A similar trend is evidence in death and transplant reports, as you will see later in the presentation. This has occurred despite an ever increasing number of patients who are exposed to the drug each month. This decreasing incidence is due in part to the recommended monitoring, but perhaps more

importantly it's due to the very high awareness of this problem that has been generated and shown in surveys of prescribing physicians.

In today's presentation, we will outline the reasons which we believe that the benefits of Rezulin in the treatment of Type 2 diabetes clearly outweigh the highly publicized risks.

Following this brief presentation, Dr. Paul Watkins, Professor of Medicine and Professor of Pharmacology at the University of Michigan, who is a well recognized expert in hepatology and drug metabolism and has systematically reviewed these cases for us, will describe our current state of knowledge of the pathology, time course, and possible pathologic mechanisms of these idiosyncratic liver events.

Dr. Mark Pierce, Vice President of Clinical Research and Parke-Davis will discuss our estimate of incidence and the positive impact of label changes on these incidence estimates.

Dr. Gerry Faich, who is formerly head of the Drug Postmarketing Surveillance at the FDA and is currently President of Pharmaceutical Safety Assessment, has assisted us in this analysis and will join Dr. Pierce in the presentation.

Drs. Pierce and Faich will show a

different picture than that that has been portrayed by earlier presentations, and they will show that these events are rare, and the rate is decreasing.

Dr. Philip Home, Professor of Diabetes Medicine and Endocrinology at the University of Newcastle in Great Britain and Vice President of the International Diabetes Federation, will discuss the comparative risk of troglitazone. Dr. Home, who has researched and published in the spectrum of therapies in diabetes will present data which show that the risk of Rezulin treatment is comparable to the risk of therapy with other agents available to patients with Type 2 diabetes.

Dr. Randy Whitcomb, Vice President of Clinical Research at Parke-Davis, will present a summary of the data that demonstrate the benefits of Rezulin therapy in a wide range of Type 2 diabetes patients.

And finally, I will conclude the session with an overall summary and assessment of the risk-benefit ratio, which we feel remains quite positive.

In addition to the presenters, the following additional consultants will be available for comment:

Dr. Thomas Buchanan, Associate Professor

of Medicine at USC;

Dr. Andrew Drexler, Director of the Mount Sinai Medical Center;

Dr. Judith Jones, former Director, Division of Drug Experience at the FDA, and currently President of the Degge Group. Dr. Jones has some valuable information which we will try to include in our presentation. If that's not possible, we would be very happy to present it in the discussion period. It is relates to an employee database cohort looking at the background incidence and comparative risk of liver events in treatments for Type 2 diabetes.

Dr. Chris O'Conner, Associate Professor of Medicine at Duke University.

Dr. Jerry Olefsky, Professor of Medicine and Head of Endocrinology and Metabolism at UC, San Diego.

And Dr. Ken Polonsky, who also helped us in the evaluation of this, was unfortunately unable to join us, but he's head of medicine and head of the Division of Endocrinology at the University of Chicago.

Our series of presentations will clearly demonstrate that the risk of liver related death and transplant is low and declining. The risk compares

favorably to the risk of serious events associated with other available treatments; that physicians have a high awareness of the risk and the need for monitoring; and that Rezulin through its unique mechanism provides marked benefit in combination and in monotherapy to hundreds of thousands of patients.

I'd now like to introduce Dr. Paul Watkins, Professor of Medicine and Professor of Pharmacology at the University of Michigan, to provide a description of the liver events with troglitazone.

DR. WATKINS: I am Professor of Medicine and Professor of Pharmacology and Director of the Clinical Research Center at University of Michigan. I am practicing hepatologist there.

I have consulted at some time with most of the major pharmaceutical companies, and I've listed here the active consulting contracts I have. I do not receive, own stock in or receive research support from any of these companies, including Warner-Lambert, Parke-Davis. I also have a consulting contract with the Food and Drug Administration, but have not consulted with them on issues related to troglitazone.

By way of background, what we are talking about here is hepatocellular injury. This is when a drug or the metabolite of the drug injures the liver

cell in a global fashion, causing liver cells to leak or die, breaking open, releasing their contents into the blood, and that content included alanine amino transferase or ALT.

In an otherwise healthy liver, the height of the serum ALT should correlate with the extent of injury that's occurring, and by convention, three times the upper limit of normal has been considered clinically significant, although the actual degree of injury occurring at that level is quite mild.

When jaundice occurs in an hepatocellular injury as opposed to other types of injury, severe liver injury has occurred, and the purpose of ALT monitoring is to prevent the onset of jaundice.

This is a typical patient manifesting ALT elevations in the clinical trials, and what's shown here in light blue is the serum ALT as a function of time on drug with monthly monitoring, and as was characteristic, there was no evidence of liver injury until in this patient about four months on drug when the serum ALT gradually rose.

The drug was discontinued. You may not be able to see the yellow line there, and then the serum ALT returned to normal, indicating resolution of the liver injury.

Characteristically in the clinical trials, the ALT elevations were between two and seven months on drug.

Now, the rationale for monitoring is that by catching the ALT rise before jaundice -- you can see the bilirubin was not affected, shown in orange -- you prevent progressive liver disease to jaundice and perhaps worse. So you would assume that stopping the drug at this point prevented the progression of disease, and certainly that appears to be the case in some individuals.

However, we were able to learn from the clinical trials that that's not always the case, and that was because in the pre-approval clinical trials, or most of them, there were no stopping criteria based on ALT, and ALT elevations were generally asymptomatic. So that in about half of the patients who developed an ALT elevation greater than three times the upper limit of normal, the physician elected to continue therapy with the drug.

And what's shown on this slide is one such patient who manifested the typical elevation -- this is a constricted time scale -- over a couple of months, then had the serum ALT return to normal, but in fact, stayed on the drug until almost two years

later when the study was discontinued.

And actually there were five patients in the clinical trials treated through ALT elevations greater than ten times the upper limit of normal. When the serum ALT returns to normal with this type of injury, the liver is normal, and there was never any change in the serum bilirubin, and what this tells us is that with this drug, as with other drugs such as propathyaurasil tacrin, the liver does have the ability to adapt to the initial injury.

We are forced, however, to stop all people whose ALTs elevate because we don't know which subset -- we're incapable of identifying them that will go on to an aggressive injury.

Now, I was brought in immediately after the first severe liver event was noted postmarketing in the fall of 1997, and since then I've reviewed all Med Watch reports of liver related events on a weekly basis.

In the last several months we formed a team. That's myself and two other hepatologists at the University of Michigan, who have contacted the institutions, tried to speak to the relevant physicians, to obtain complete information on all the cases.