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FOOD AND DRUG ADMINISTRATION

FDA GENETIC TOXICOLOGY WORKSHOP

How many doses of an Ames-positive/Mutagenic
(DNA Reactive) Drug can be safely administered
to Healthy Subjects?

PRESENTATIONS & PANEL DISCUSSION

DATE: Monday, November 4, 2019

TIME: 8:30 a.m.

LOCATION: FDA White Oak Campus
Building 2 (CSU), Room 2031
10903 New Hampshire Avenue
Silver Spring, MD 20993

REPORTED BY: KeVon Congo, Notary Public

JOB No.: 3418719

1 P A R T I C I P A N T S

2 Presenters:

3 Dr. Timothy W. Robison, CDER, FDA

4 Dr. Kevin Prohaska, CDER, FDA

5 Dr. Bob Dorsam, CDER, Office of Generics, FDA

6 Dr. Dayton Petibone, NCTR, FDA

7 Dr. Jennifer Shemansky, NCTR, FDA

8 Dr. Douglas Brash, Yale University

9 Dr. Kenny Crump, Louisiana Tech University

10

11 Panelists:

12 Dr. Aisar Atrakchi, CDER, FDA, Moderator

13 Dr. Alan Boobis, Imperial College London

14 Dr. Douglas Brash, Yale University

15 Dr. Kenny Crump, Louisiana Tech University

16 Dr. Robert Heflich, National Center for Toxicologic

17 Research, FDA

18 Dr. Timothy McGovern, CDER, FDA

19 Dr. Miriam C. Poirier, National Cancer Institute, NIH

20 Dr. Kevin A. Prohaska, FDA

21 Dr. Errol Zeiger, Private Consultant

22

1 DR. TIMOTHY ROBISON: Good morning.
2 This is the Genetic Toxicology Workshop. I just have
3 a few sort of general announcements.

4 Just to note that this is a public
5 workshop. Both members of the public and FDA staff
6 are present. So no proprietary information should be
7 discussed.

8 The workshop is being recorded and a
9 transcriptionist is present to transcribe everything
10 that is said.

11 The workshop serves as an educational
12 event for FDA staff and the public. Further, it's a
13 forum to seek advice from an expert panel on several
14 questions. We have a panel discussion in the
15 afternoon. There will be open question periods during
16 the meeting, both FDA staff as well as the public are
17 invited to ask questions.

18 I would just like to extend thank-you's
19 to the Genetic Toxicology Subcommittee, the National
20 Center for Toxicological Research, the Office of Generic
21 Drugs, and Division of Hematology, Oncology, and
22 Toxicology, the Pharm-Tox Coordinating Committee, and

1 Pharm-Tox Coordinating Committee Educational
2 Subcommittee, who all helped with this workshop.

3 The overarching question of this
4 workshop is how many doses of an Ames-positive,
5 mutagenic, or DNA-reactive drug can be safely
6 administered in healthy subjects.

7 Healthy subjects are commonly enrolled
8 in human Phase I clinical trials of new drug
9 candidates under an IMD. So these studies are
10 typically short. They can range from two days to a
11 few weeks. The treatment may be continuous or
12 intermittent. And since intermittent, there could be
13 a washout period between each dose. Typically this
14 washout period might be up to five half-lives.

15 Just to note as an important
16 consideration is that these healthy subjects received
17 no benefit and are potentially exposed to significant
18 health risks in the proposed trial. Patients will be
19 enrolled in longer Phase 2 and Phase 3 clinical
20 trials. Our focus is primarily on Phase 1 where
21 healthy subjects are enrolled.

22 Advantages of conducting trials in

1 healthy subjects include investigations of
2 pharmacokinetics, bioavailability, and the absence of
3 other potentially confounding drugs, data not
4 confounded by disease, identification of maximum
5 tolerated dose, reduction in patient exposure to
6 ineffective drugs or doses, and rapid accrual into a
7 study.

8 Just from personal experience, there
9 are a number of disease indications where patients are
10 fully subscribed and it's very difficult to find --
11 it's a very slow process to find patients with -- in
12 some ways it's much easier to recruit healthy
13 subjects.

14 Our new IND, the supporting
15 (indiscernible) receive a fairly extensive non-
16 clinical data package that lists the studies here.
17 I'd like to focus on the toxicology studies, which
18 typically range in duration from 14 to 28 days and
19 they are conducted in both rodent and non-rodent.
20 Also there is a standard battery in genetic toxicology
21 studies. This includes an Ames Bacterial Reverse
22 Mutation Assay. That could mean for a single dose.

1 And then for a repeat dose, it would also be an
2 invitro mammalian cell gene-tox assay.

3 And prior to the start of Phase II
4 trials would receive an invitro micronucleus study.
5 Primarily in Phase I trials you primarily would have
6 the Ames assay and an invitro mammalian cell assay.

7 The toxicology studies are used
8 primarily to set clinical doses using -- based on the
9 findings of animal study in terms of dose
10 (indiscernible) toxicity and target (indiscernible) or
11 toxicity. This information is also used to assist
12 with clinical monitoring.

13 The genetic toxicology studies are used
14 for hazard identification to get a general sense of --
15 if it's a mutagen or a clastogen. Cancer drugs are
16 often presumed to be genotoxic. The genetic
17 toxicology (indiscernible) are not generally required
18 for clinical trials in cancer patients.

19 Generally most drugs that are found to
20 be positive for mutagenicity, i.e. Ames positive,
21 outside of oncology indications are not developed and
22 generally drop from development.

1 The ICH M3(R2) guidance provides
2 follow-up for a positive invitro mammalian cell
3 chromosomal aberration assay in the sense of
4 conducting two in vivo mammalian assays typically in
5 in vivo micronucleus tests and in vivo liver common
6 assay, two in vivo assays with two endpoints.

7 However, the Ames test results are
8 thought to indicate (indiscernible) reactivity and
9 extensive follow-up testing to assess in vivo
10 mutagenetic and carcinogenic potential would be
11 warranted to assess the potential risk for treatment
12 that's justified by appropriate risk-benefit analysis.
13 I think it's our general thought that a positive Ames
14 assay has a high correlation to tumor findings in a
15 two-year rodent bioassay.

16 However, in the U.S., a drug with a
17 positive in vitro Ames bacterial mutagenicity assay
18 may still be administered in healthy subjects and are
19 enrolled in the single dose clinical trial if they are
20 not made aware of the study results in the informed
21 consent.

22 One of the dilemmas that has come up is

1 that pharmacokinetic studies typically require at
2 least two to four doses, such as a crossover design.
3 Dr. Dorsam will go a little more into detail of this
4 later. This has sort of led to questions about the
5 risk with a small number of doses beyond a single
6 dose.

7 And just to note that there can be --
8 still these can be separated by washout period or that
9 could be continuously dosed by a number of daily
10 doses.

11 This sort of leads to the question of
12 how many doses of a reactive drug can be safely
13 administered to healthy subjects. Does this concern
14 for an Ames-positive drug only applied to chronic
15 administration or does it extend to a small number of
16 doses, i.e. one, two, three, or four doses? The
17 worst-case scenario might be 14 daily doses.

18 There is a acknowledge of published
19 literature or guidance, documents directed towards
20 trying to understand the cancer risk or other
21 potential health concerns associated with a small
22 number of doses of an Ames-positive drug in healthy

1 subjects.

2 Just to note that results of rodent
3 carcinogenicity studies with a new drug candidate are
4 typically not available until late in drug
5 development. We normally wouldn't receive them until
6 the sponsor files a new drug application.
7 Applications will come in very late in Phase III
8 trials. During the IND development stage, we are
9 principally reliant on the standard battery of genetic
10 toxicology studies to sort of inform the potential for
11 cancer. Several review divisions do allow a single
12 dose of an Ames-Positive drug in healthy subjects.
13 However, others do not allow any dosing. And yet some
14 others may allow more than one dose. Several review
15 divisions have raised questions regarding the number
16 of doses of an Ames-positive drug they can safely
17 administer to healthy subjects.

18 Today CDER is seeking advice of a panel
19 of experts. Again, the overarching question for the
20 workshop is how many doses of an Ames-Positive drug
21 can be safely administered to healthy subjects.

22 We did reach out to Health Canada,

1 Japan, and EMA to get some understanding of their
2 practice for dealing with an Ames-positive drug.
3 Health Canada replied that a clinical trial in healthy
4 subjects with an Ames-positive drug would not be
5 allowed to proceed without substantial follow-up
6 testing to demonstrate that the drug is not mutagenic
7 in vivo. In Japan, they did not allow administration
8 of a clearly Ames-positive drug in healthy subjects.
9 They do note in the ICH M3(R2) guidance that it's
10 permissible to allow a small number of microdoses.
11 This is a dose of approximately 100 microgram per day.
12 It's not a pharmacologically active dose, but
13 potentially it could allow up to five doses at a dose
14 of 100 microgram per day. Again, this is not a
15 pharmacologically active dose. It's more than ten to
16 a thousand fold lower than a pharmacologically active
17 dose that would be commonly used in a clinical trial.

18 Also, they note that they would have
19 less concern if the drugs has no structural alerts and
20 that there is less concern where it will be Ames-
21 positive if it does not possess structural alerts when
22 considering mutagenicity.

1 Bay Pharma in Germany noted they have
2 not dealt yet with this issue with applications for a
3 first human trials with Ames-positive drug candidates
4 outside of the microdosing scenario.

5 MHRA UK said they would consider
6 scientific justification as to why a sponsor thought
7 it was acceptable to dose healthy volunteers with a
8 product that was genotoxic, e.g. positive in the Ames
9 test. The sponsor would need to provide specific
10 justification as to why to conduct further -- evaluate
11 -- further studies to evaluate the genotoxic potential
12 of the product and the associated clinical relevance.

13 Examples are given in ICH S2(R1). A
14 single dose first in human trial with an Ames-positive
15 drug may be acceptable providing that there is
16 adequate justification listed and a number of things
17 based on the threshold of toxicological concern, the
18 half-life, the proposed clinical dose, the strains in
19 which the drugs was positive in the Ames Assay. They
20 sort of would be very negative about a dosing out to a
21 week with an Ames-positive drug.

22 So today we have a series of

1 presentations. I'm providing an introduction. I will
2 be followed by Dr. Kevin Prohaska, who will speak
3 about the FDA requirements for protection of healthy
4 subjects in Phase I clinical trials. This will be
5 followed by Dr. Bob Dorsam from the Office of Generic
6 Drugs, looking at the Considerations for a Genotoxic
7 API in Clinical Trials: Healthy Subjects or Patients?

8 Doctors Dayton Petibone and Jennifer
9 Shemansky at NCTR have conducted an extensive
10 literature review. And Dr. Petibone will present as
11 well as this literature sort of to try to get a bit of
12 -- Dr. Petibone will explain more about trying to
13 understand the risks of a small number of doses of
14 Ames-positive drug, to see what's available in the
15 literature. They conducted a search more or less for
16 the past year, going through thousands of articles to
17 glean out information that might be helpful.

18 This will be followed by a presentation
19 by Dr. Douglas Brash from Yale University, Do the
20 Steps between Genotoxin and Cancer Create Thresholds
21 of Dose or Time?

22 I have to note that Dr. Crump wasn't

1 able to make it today due to a death in the family.
2 I'm going to try to give a very brief presentation
3 that highlights his talk. He did send a video, and
4 I'll see if it's possible to send that video at a
5 later date. We weren't able to -- we just received it
6 last night and we weren't able to have it ready today.

7 In the afternoon, we're having a panel
8 discussion. We brought together a panel of
9 international experts. If you look at the more
10 extended agenda, there is a bio sketch for each of
11 these individuals. They will also introduce
12 themselves at the start of a panel discussion this
13 afternoon.

14 For today's discussion of DNA-reactive
15 drugs, we have chosen to principally focus on Ames-
16 positive drugs since there is a high correlation
17 between chemicals found in positive assay and the
18 positive Tumorigenicity findings in the two year
19 rodent bioassay. We're assuming that the drug has the
20 potential to be DNA reactive and form DNA adducts that
21 can induce strand breaks or intercalate in between the
22 DNA bases.

1 We note that the many potent genotoxic
2 carcinogens can be positive for both mutation and Ames
3 assay as well as positive for clastogenicity, wouldn't
4 necessarily be that uncommon if they were positive
5 (indiscernible) more than one assay of the standard
6 battery. Dr. Petibone will provide some supportive
7 information.

8 I'm going to briefly talk about how
9 mutations may cause cancer. And this is sort of going
10 through the literature to sort of provide a hypothesis
11 on how this might occur. It's not to try to exclude
12 other mechanisms or other potential paths, just to
13 sort of give a general overview.

14 DNA damage is an important first step
15 in the carcinogenesis process. Chemical carcinogens
16 can cause the formation of DNA adducts. They can
17 induce other modifications to DNA, such as oxidative
18 damage and alterations to DNA, alter structure.

19 In the cartoon I'm showing benzopyrene.
20 It can undergo metabolic (indiscernible) to form a
21 reactive epoxide. It also could be potentially be
22 detoxified by enzymes in the cell or it can go on to

1 interact with DNA and form a DNA adduct. There is a
2 possibility for DNA repair to remove the adduct. But
3 what we're focusing on today is that it forms -- will
4 react with DNA to form an adduct. And you can see the
5 (indiscernible) the DNA structure. Potentially these
6 changes in DNA could potentially go on and lead to the
7 generation of the tumor.

8 Cells do (indiscernible) mechanisms to
9 repair many times with DNA damage. However, these are
10 not always completely effective. The majority of
11 mutations may be largely neutral in that they're
12 passenger mutations. However, mutations in an
13 oncogene, tumor suppressor gene, or a gene that
14 controls cell cycle can result in a (indiscernible)
15 cell population that the proliferation or survival
16 advantage. These mutations are known as drivers, and
17 driver genes are defined as genes containing driver
18 mutations. Oncogenes are defined as driver genes in
19 which the driver mutations are activating or result in
20 new functions. Tumor suppressors are driver genes in
21 which the driver mutations are inactivating.
22 Oncogenes tend to be affected by vocal amplifications

1 or (indiscernible) mutations (indiscernible) limited
2 number of codons. Tumor suppressors tend to be
3 affected by (indiscernible), frameshift, or splice-
4 site mutations (indiscernible).

5 The specific types of activating or
6 inactivating mutations can be specific to a driver
7 gene. Gene rearrangements almost exclusively activate
8 the oncogene in non-Hodgkin's lymphoma. The
9 (indiscernible) the cause of (indiscernible) oncogene
10 activation.

11 There are always some pre-existing
12 mutations, some of which amplify in the tissue because
13 of their driver genes. Mutagens induce additional
14 mutations (indiscernible) so the passenger mutations
15 generally greatly outnumber driver mutations. Some
16 driver mutations occur in DNA repair or replication of
17 genes and induce a mutator phenotype which results in
18 additional driver and passenger mutations with each
19 cell division. Transformation from a normal to a
20 tumor requires accumulation of five to eight driver
21 mutations in the same cell. I have seen publications
22 where it was noted that it might be as few as three

1 driver mutations.

2 If most have accumulated already, an
3 unlocking mutation induced by a single exposure has a
4 small but measurable chance of initiating the tumor.
5 And single mutation cancers are known -- single
6 rearrangement to form. The Philadelphia chromosome is
7 probably all that is needed to cause a chronic myeloid
8 leukemia.

9 The gold standard of evidence that a
10 mutation is a driver is that the mutation produces a
11 cellular phenotype introduced to a selective advantage
12 to the cells harboring it. And such phenotypes may be
13 directly or indirectly to the survival and
14 proliferation and clonal expansion of mutant daughter
15 cells. Each create a pair of mutant daughters,
16 exponentially increasing the prevalence of mutant
17 cells.

18 From initiation you can have a
19 polyclonal expansion, you can have clonal
20 cooperativity. There is some shown in the diagram.
21 Dr. Brash is going to go on to this in more detail.
22 But I think it's well-known that epithelial cells,

1 (indiscernible) cells, immune cells can potentially
2 cooperate and lead to expansion of the tumor.

3 Just sort of moving on, there is quite
4 a bit of literature that a single exposure to a
5 carcinogen can lead to cancer. There is a published
6 study with 426 agents. You can see there is a diverse
7 set of chemicals, polyaromatic hydrocarbons,
8 (indiscernible). So there is quite a bit of
9 literature that a single exposure can lead to cancer.

10 I just wanted to briefly note, just
11 sort of moving on to intermittent exposure to
12 pharmacokinetic study with the drug administered to
13 healthy subjects. Doses are typically separated by a
14 washout period. We mentioned up to five half-lives
15 were created in 95 percent of the drug,
16 (indiscernible) be cleared. Considering the number of
17 days of treatment, there are intermittent exposures
18 where there is a washout period between treatment.
19 There is a greater probability that the drug could
20 never reach study's date. There's sort of -- just
21 looking at the mode of action, there is a recovery
22 time. This could decrease the potential risk of a

1 genotoxic adverse health outcome. Continuous exposure
2 could saturate DNA repair capacity or other
3 physiological processes, whereas intermittent
4 exposures would allow for DNA repair or other adaptive
5 or invisible physiological responses. Therefore
6 approach for intermittent exposures is to consider the
7 potential for repeated exposure during a lifetime and
8 we combine these into an equivalent short-term
9 scenario. And finally, apply the same approach for
10 that of the short-term exposure.

11 I just wanted to get to our concern to
12 the single dose. Which is sort of how I see
13 (indiscernible) might deal with this. Use of drugs
14 that are genotoxic based on this battery of tests in
15 healthy subjects. These subjects are exposed to all
16 risk and no benefit. The minimized risk to healthy
17 subjects of a virtually safe dose of a genotoxic
18 carcinogen has generally been defined as a dose which
19 after a lifetime exposure would result in one
20 additional cancer case in a population of one million.
21 Assuming for a 70-year life span, there is 25,000
22 days. The linear extrapolation of a virtually safe

1 dose to a one or ten-day exposure results in a daily
2 dose level of 25,000 times the virtually safe dose, or
3 2,500 times the virtually safe dose, at which
4 exposure's lifetime risk is considered acceptable. If
5 sensitive populations can be identified, an additional
6 dose correction factor of ten is applied resulting in
7 a tenfold lower daily dose. At these dose levels, the
8 additional lifetime cancer risk is considered to be
9 negligible since they are set for susceptible cell
10 populations.

11 And I think I'm going to stop here. I
12 have a few minutes for questions if there are any.
13 We'll move on. If there are no questions, we can just
14 move on to the next presentation. Are there any
15 online questions?

16 WOMAN: Will the slides be available
17 after the --

18 DR. TIMOTHY ROBISON: Yes, yes.

19 Our next speaker is Dr. Kevin Prohaska.
20 He is a bioethicist here at FDA. He is going to speak
21 about the FDA Requirements for the Protection of
22 Healthy Subjects in Phase 1 Clinical Trials.

1 DR. KEVIN PROHASKA: Good morning,
2 everyone. Can you all hear me? Fantastic.

3 Well, thank you very much for -- first
4 of all, thank you for inviting me to speak at this
5 meeting. But also I wanted to thank everyone for
6 showing up today. This is fantastic. To my
7 understanding there is about a hundred or so people
8 online in addition to the people here. So this is a
9 great showing. Thank you very much. This is a very
10 important topic, and we certainly want to try to get
11 some good recommendations at the end of the day so
12 that we can help this important research go forward.

13 What I've been tasked to talk about
14 today is the FDA Requirements for the Protection of
15 Healthy Subjects in Phase 1 Clinical Trials. And I
16 also want to clarify that as far as my ethics
17 consultation works go, my focus is in adult research.
18 We do have two pediatric ethicists who are involved in
19 focusing on pediatric research. There we go.

20 And then the usual disclosures. The
21 opinions that I am going to present today are my own.
22 Especially later when we're having Q&As, I'm likely to

1 hopefully spill into some issues that might not
2 necessarily reflect the FDA, although I hope they do.
3 And the objectives are to provide a general overview
4 of the FDA requirements for the protection of healthy
5 subjects and also to give you an overview of the
6 ethical principals that are considered when I look at
7 Phase 1 clinical trials offering no prospect or direct
8 benefit to healthy subjects, which is primarily the
9 focus of today's conversation.

10 Now, of course most everybody here,
11 especially within the FDA, are familiar with this
12 classic drug development outline if you will. The
13 important point about this is we are going to be
14 focusing on strictly the Phase 1 aspect of this
15 development program. However, as we all know, the
16 phase are starting to blend into each other. And a
17 lot of groups are doing Phase 1 work and Phase 2 and
18 then Phase 3 and so forth and so on. And that's an
19 important point to remember, because sometimes it can
20 complicate the analysis that's necessary for the
21 ethics of all of this. But we're going to confine our
22 conversations to the Phase 1 in the classic sense.

1 So the concerns that we have from a
2 bioethical point of view are pretty straightforward.
3 Phase 1 clinical trials do not typically offer the
4 product of direct benefit of the subjects. The
5 healthy subject is not likely to benefit from the
6 product development because they don't have the target
7 condition. Now, ideally it would be nice if you
8 actually were to enroll people at risk for the
9 condition, albeit healthy. That would actually
10 facilitate some of the risk discussion that might
11 occur.

12 Pre-clinical work may be suggestive of
13 safety signal. And that's the focus of today's
14 conversation of course with the Ames studies. And we
15 need to assure that healthy subjects are not unduly
16 influenced in participating in the research. Undue
17 influence is sort of a nebulous phrase, and it's sort
18 of hard to pin down what exactly we mean by that. So
19 it's another one of those areas where we have to use a
20 lot of judgement.

21 And consent document. Again, the
22 process needs to be clear and balanced and minimize

1 misunderstandings and undue influence.

2 So as most everybody here knows, the
3 IND content has a lot of different things that are
4 required. And the point of this slide was that here
5 at the FDA when you submit these IND applications to
6 us, it crosses multiple disciplines, including ethics.
7 And I probably get brought in on a minority of these,
8 but when ethical issues arise from the initial review
9 of these applications, they asked me to come in and
10 give my opinions. And that's about 80 percent of the
11 work.

12 Now, the regulations for the protection
13 of human subjects are primarily confined to two areas,
14 Part 50 and 56. Part 50 are the ones that have to do
15 with the informed consent for the most part, and 56
16 have to do with the IRB responsibilities.

17 Now, I raise that as only part of the
18 human subjects protection, because I would argue Part
19 312 and all the other parts also have embedded in it
20 human subject protection concerns. That's why we
21 asked for all of this safety information, because we
22 want to protect people. So that's very important to

1 keep in mind.

2 So there are no specific unique human
3 subject protection regulations that apply to research
4 involving healthy subjects. So that's a point that I
5 wanted to make.

6 What happens is we have to think about
7 the general recommendations and how it applies to the
8 population that's being enrolled in the study. And it
9 doesn't matter what population it is, whether you're
10 talking about a vulnerable population or say
11 cognitively impaired individuals, or in this case
12 healthy individuals, or maybe the full spectrum in
13 between.

14 Our regulations are based on the work
15 that was outlined in the Belmont report. And there's
16 three principles that we think about. There's respect
17 for persons, beneficence, and justice. Now, there's a
18 lot of different ways of trying to carve up the
19 bioethics if you will. But this is the foundation on
20 which our regulations are developed. And I should say
21 that that developed in response to the Tuskegee events
22 in the 20th century.

1 So, respect for persons come from the
2 requirements from the informed consent. The
3 additional protections that we have for vulnerable
4 populations that we have, like say for subpart D for
5 pediatric research is a good example. And then
6 there's a growing concern about privacy and
7 confidentiality, especially in this day and age with
8 big data and whatnot, that it seems to be growing even
9 more lately.

10 Beneficence. We want to make certain
11 that risks for subjects are reasonable in relationship
12 to anticipated benefit. In this particular case, we
13 don't have benefit to the individual, so we have to
14 consider it in relationship to the social value that
15 the research offers to the community, to public
16 health. And then the risk benefit is that it has to
17 be at least as favorable as available alternative
18 approaches. So that's sort of a question I ask; how
19 would this product compare to the other things that
20 were available on the market? You know, if it's just
21 a me-too drug, then why are we exposing people to a
22 lot of different risk when there's 20 other me-too's

1 in that category. If it's a unique drug and it looks
2 like it's going to offer great promise, then it is an
3 area where we might consider some additional risks
4 that we wouldn't necessarily consider otherwise.

5 Again, we have to always worry about
6 the qualification, not only of the investigator, but
7 everybody else that's involved with the research. So
8 that's sort of something we consider as well. And
9 then trial design, critically important. If the trial
10 is not adequately designed, if it's not scientifically
11 sound, then I would argue that there's really no good
12 reason to expose anybody to any level of risk, because
13 you're not going to learn something at the end of the
14 day. Very important to consider.

15 And then justice. We want to make
16 certain that the selection of subjects is equitable,
17 that when the population is not exposing all the risks
18 for the benefit of another group or population. The
19 exclusion criteria is reasonable and the recruitment
20 efforts are appropriate.

21 I'll go over this quickly. In Part 56
22 there's a whole bunch of criteria that the IRB uses

1 for reviewing research. The one that I think is going
2 to be the focus of today's conversation is the second
3 element. This is the paraphrase that the risk to
4 subject is reasonable in relationship to the
5 anticipated benefit. Again, we don't have benefit
6 here, so we're thinking about social value. And the
7 importance of the information that may be expected to
8 result.

9 So a couple of things related to FDA
10 policies. The FDA does not consider payment to
11 subject as a benefit. So that is not something that
12 we -- say, well, they're getting paid a lot of money
13 to do this research, so they can get the risk. That's
14 off the table. That's not part of the conversation.
15 We do want people to be adequately compensated for the
16 time and effort that they're doing of course. But
17 they're not being paid per se to be exposed to lots of
18 risk.

19 Risks should be considered in the
20 context of the social value. I've said that a couple
21 of times.

22 Social value could be thought of as the

1 goal to have research hypothesis that asks an
2 important question. For Phase 1 trials, the
3 expectations would be that the study contributes in a
4 significant way to the development plan of the
5 investigational product. So we know we're at the
6 beginning of the process, and there's a lot to be
7 done. But you have to get started somewhere. But the
8 Phase 1 trial needs to ask some important hypotheses.

9 But there are limits as to how much
10 risk can be justified by social value alone. Many
11 ethicists believe that potential harm should not be
12 irreversible, lead to permanent disability, or
13 potentially fatal. Others believe that there is a
14 need to balance paternalism with autonomy. And for
15 me, it's very helpful to codify the risk whenever
16 possible. I know that it's extremely difficult to
17 quantify risk in any substantial way. But when that
18 can be done, it's very helpful to try to help with the
19 analysis. It almost always comes down to a judgment
20 call.

21 This slide is interesting. The concept
22 of paternalism and autonomy are ethic concepts that

1 have always been in conflict with each other in some
2 ways. And what I wanted to present here was the
3 evolution over time that's happened since the end of
4 World War II with the Nuremburg Code all the way up to
5 the CIOMS guidance in 2016. There has been a greater
6 understanding that there are sometimes appropriate to
7 move forward with doing some research when there's no
8 prospect of direct benefit. Unfortunately, none of
9 these ethical codes sort of quantify what's the
10 acceptable level of risk, while they do sort of
11 support the use of some research in this population.
12 Except for the Nuremburg Code. And the Nuremburg Code
13 was funny in the sense that it sort of suggested that
14 they start experimenting on the investigator, which is
15 interesting. But I think that that was certainly an
16 outcome of the atrocities of World War II.

17 So the general requirements for
18 informed consent. Most everybody here knows all this
19 stuff. The investigator shall seek consent only under
20 circumstances that provides prospective subjects or
21 their representatives, their legally-authorized
22 representatives, sufficient opportunity to consider

1 whether or not to participate and that minimize the
2 possibility of coercion or undue influence. The
3 reason I read that is because it's a critically
4 important sentence to unpack.

5 Coercion I'm going to take off the
6 table. And what that basically means is that there is
7 a threat going on. And obviously there should be no
8 research going to the FDA in which there is a sense of
9 threat. But undue influence is a nuanced phrase that
10 requires some unpacking and some thinking about to
11 determine whether or not it's occurring.

12 What this sentence reminds me of is
13 that not only are the elements of constant important -
14 - and there are currently eight of them in the FDA
15 regulations -- but that the context in which consent
16 is obtained and how it's obtained is critically
17 important. People ought to be given time when it's
18 appropriate, be given time to think about it. If
19 there is a very high level of risk, we want to make
20 certain people understand what that risk is. And
21 there's ways of doing that for the consent process by
22 test backing and things of that sort to make certain

1 they understand.

2 So then there's other things you want
3 to do. Then there's the issue of compensation for
4 injuries is one of those controversial things that we
5 sometimes have to deal with. The right to withdraw at
6 any time must always be respected. Now of course
7 there are some research protocols in which it may not
8 be safe for people to abruptly stop, in which case
9 that's part of the consent process. So making them
10 understand that they need to table off the drug or be
11 followed by a short period of time for their own
12 safety. But at the end of the day, people should be
13 allowed or must be allowed to withdraw at any time.

14 I'm not going to go over these, but
15 these are the consent elements. They're under 50.25,
16 the required basic elements under 50.15(a). The
17 additional elements are the ones that IRBs consider
18 including when the conditions are appropriate. And
19 then the applicable clinical trials is 25
20 (indiscernible). And that's that verbatim statement
21 that has to be in the consent document for any
22 applicable clinical trial.

1 As far as the consent document goes,
2 when I look at them, I want to make certain that the
3 risk discussion is very clear, that significant risks
4 should be emphasized, that you might want to consider
5 a test to assess people's understanding of the risk
6 when they are substantial or difficult to understand.
7 Statements about lack of benefit must be clear. Do
8 not conflate the payments of other healthcare services
9 provided during a trial. That's important. The
10 social value can be scribed, but it must be balanced.
11 You want to avoid overly-optimistic or misleading
12 statements when you do craft these consent documents.
13 And the amount and process for paying subjects should
14 be described of when creating undue influence.

15 Here one of the things that can happen
16 is if all the payment is weighted until the end and
17 you must finish the (indiscernible) if you're going to
18 get anything. Well, that may not be fair if it's a
19 multi-visit study. So perhaps the payments should be
20 staggered so that they won't feel compelled to finish
21 the research if they don't want to.

22 Grounds for clinical holds. You all

1 know this. But the one that I point out every once in
2 a while. We all think about safety, but we also have
3 to keep in mind that scientific soundness is also a
4 ground for clinical hold. So, unreasonable
5 significant risk is the one that I sometimes get
6 pulled into, and it's a judgment call.

7 So what do I look for when I'm asked to
8 look at these things? I want to know are the risks
9 reasonable, minimized, and justified by the potential
10 social value of the trial.

11 Two, are vulnerable populations
12 protected, meaning what sort of efforts are done to
13 mitigate (indiscernible). Are people being allowed
14 enough time to look at the consent document? If
15 they're cognitively impaired, are their families
16 involved? Is there a robust informed consent document
17 in process? So that goes along with what I said about
18 number three.

19 Is the level of compensation adequate
20 and not undue? Is their right to withdraw respected?
21 Have independent experts reviewed and conducted -- I
22 did check this. I don't know what happened. Have

1 independent experts reviewed and conducted -- this is
2 sometimes very helpful and something I look for in
3 applications and protocols. In trials that are likely
4 to be controversial, it's very helpful to have
5 independent experts look at it and give their opinion
6 and may sway judgements internally. Is there a system
7 for compensation for an injury? Is there adequate
8 safety monitoring, both short-term and long-term? And
9 in this we give a case where there is concern about
10 cancer potential, long-term monitoring may be
11 appropriate.

12 Are there alternative approaches or
13 populations that would be more justifiable? And this
14 is actually a big area where I spend some time
15 thinking about it. The question really has to be
16 asked; must it be done in people who have no
17 prospective direct benefit? Can it be done in people
18 who have the condition when possible? Because that
19 can justify more risk because you would hopefully
20 benefit from the potential administration of the drug.
21 If not the people who have the condition, potentially
22 how about the people who are at risk for the

1 condition? Maybe not as much risk, but more risk than
2 a purely healthy population. So that's something to
3 think about. There may be scientific reasons for
4 doing it in healthy volunteers, and that ought to be
5 explained so that we understand what the rationale is
6 for exposing this population to these potentially
7 dangerous drugs.

8 And I put that one there to remind you
9 that this is all judgement and it's a balancing sort
10 of act that you have to weigh all of these things
11 together. And reasonable people can disagree. And so
12 risk is an area where we all have different risk
13 thresholds of what we think is tolerable. And I
14 respect that, and I understand that. And it's
15 important to just hear people out and to understand
16 where they're coming from. But at the end of the day
17 what we have to do is we have to assure that we're
18 moving forward in a reasonable way that respects the
19 individuals that are involved in this research.

20 So, thank you. I think I have time for
21 questions. Yes, I do.

22 At the end of my slides, and I think

1 you all have my slides, I put out a link to a number
2 of different resources that you might find helpful,
3 ones that I looked at while I was creating this slide
4 deck for this.

5 Yes, sir.

6 AUDIENCE: I found your Nuremburg Code
7 thing interesting, because as a researcher I'm forced
8 to think about that. There's a whole lot of, like,
9 subliminal considerations that might actually not be
10 on my consent forms that it forces me to think about.
11 So is there any experiences (indiscernible) research
12 (indiscernible) participating in these studies?

13 DR. KEVIN PROHASKA: That's an
14 interesting question. To my knowledge, the FDA
15 doesn't have a ton of experience in that. There is
16 one experience -- and I've not prepared to think about
17 the guy's name. But the guy from Australia that
18 developed -- who had the hypothesis of H. pylori and
19 peptic ulcer diseases. He self-inoculated himself.
20 That was widely criticized by a lot of bioethicists,
21 but ultimately I think he got an award for it. He got
22 an award.

1 So attitudes change over time. But in
2 general I would not necessarily support a researcher
3 doing research on themselves or their family members
4 because of the concern for undue influence.

5 AUDIENCE: I probably should have asked
6 this question before when we were preparing for this.
7 But I was curious, have you ever encountered the
8 specific question we're dealing with previously where
9 a genotoxic drug was proposed and given to healthy
10 volunteers?

11 DR. KEVIN PROHASKA: You know, I've
12 been the agency's bioethicist now for about six or
13 seven years. And to date I have not been brought into
14 this conversation. So the answer is no. But I've
15 been brought into analogous conversations in other
16 disciplines and in other areas where Phase 1 trials
17 involving potentially risky drugs were going to be
18 given to healthy volunteers. And the analysis that I
19 outlined on my last slide there is sort of the
20 majority of what I do. You know, I want to as much as
21 possible understand why they're selecting the
22 population, could it be done in somebody who has the

1 condition? If they could possibly quantify the
2 research, that would be very helpful.

3 I should add that I've looked at the
4 literature on this in preparation for today's
5 conversation, but also for previous consultations that
6 I've done. And the literature is all over the place
7 as far as the bioethics literature as to what is the
8 level of acceptable risk. And there's no real
9 definitive answer to that question I'm afraid.

10 There's one study, and I think I gave
11 the resource for it. A gentleman by the name of
12 Resnik who in a way sort of compared it to the risk of
13 highly-risky professions like a policeman or a
14 fireman. And they, for one reason or another, choose
15 to do that type of profession, for compensation of
16 course. And we allow that as a society. So the
17 question is, why shouldn't we allow a certain amount
18 of risk in clinical research. It's an interesting --
19 he presents -- I don't know if it's his own, but he
20 presents it in his paper that I cite. And I thought
21 that was very interesting and worth considering.

22 But the physician (indiscernible) goes

1 back to the first rule of medicine is first, do no
2 harm. You know? And so I said, well, that's nice,
3 but we have to also be a little bit paternalistic and
4 make certain that we offer reasonableness.

5 AUDIENCE: So I assume these kinds of
6 issues have been discussed among ethicists before.

7 DR. KEVIN PROHASKA: Oh, absolutely.

8 AUDIENCE: And it sounds like there's
9 no consensus of opinion. It's all a matter of
10 judgement.

11 DR. KEVIN PROHASKA: It's judgement.
12 You know, what's interesting -- and maybe I shouldn't
13 say this in the public venue. But a concept or
14 understanding of risk, and even privacy now, which is
15 a big risk issue, evolves over time. And our
16 understanding changes over time. And so right now I
17 think the pendulum is swinging towards -- it's
18 somewhere in the middle I would argue, but it's
19 swinging towards respecting people's individual
20 autonomy and allowing them to choose for themselves
21 the type of research they want to be in. And that's
22 fine, and I respect that. But we also have an

1 obligation to make certain they understand what
2 they're going into. And you can go through the
3 literature yourself and see that people sometimes
4 don't understand what doctors are telling them. So
5 it's important that we evaluate that (indiscernible).

6 MAN: So it sounds like if this
7 question came to you, you'd set the bar pretty high.

8 DR. KEVIN PROHASKA: Not necessarily.
9 It depends on -- I apologize, you know, for the
10 vagueness of my response, because it really -- it's
11 the context. You know, what are the alternative
12 therapies that are available for cancer meds being
13 sought after? If there are 20 other therapies and
14 they all seem to be doing just fine, I wouldn't
15 necessarily be in favor of exposing highly risky drugs
16 to healthy people. But if it was a novel drug that
17 was going to potentially have an incredible promise,
18 then that might justify more risk. There's no one
19 factor to consider; there are other factors to
20 consider, too.

21 MAN: So one last question. Genetic
22 toxicologists love case studies.

1 DR. KEVIN PROHASKA: Right.

2 MAN: Are you aware of a collection of
3 case studies dealing with risky situations like this
4 in Phase 1?

5 DR. KEVIN PROHASKA: I'm aware of them,
6 but I've not --

7 MAN: Are they published?

8 DR. KEVIN PROHASKA: I'm sorry?

9 MAN: Are they published as case
10 studies? I can imagine health [OVERLAPPING SPEAKERS]
11 might have it. Completely different view of this than
12 the FDA.

13 DR. KEVIN PROHASKA: Well, actually, I
14 was looking at the report that was done -- Health
15 Canada seem to have a very moderate approach to this.
16 I think that they were advocating microdosing. What
17 was the presentation that preceded me? There was a
18 suggestion as to which regulatory body and what they
19 allow. You know? And I was thinking, oh, that's sort
20 of important. Certainly I would advocate for
21 microdosing wherever possible. You want to expose
22 people to the lowest dose possible and so forth.

1 MAN: My understanding is we don't like
2 microdosing for (indiscernible).

3 WOMAN: It's not really commonly used.

4 MAN: Not commonly.

5 DR. KEVIN PROHASKA: Yeah. Well, fair
6 enough. If there's a sound scientific reason for not
7 doing it, then that would be appropriate not to do it.
8 But where it can be done, it should be done.

9 DR. DAN LEVY: Hi, I'm Dan Levy from
10 the FDA Center for Foods. So I have two questions.
11 I'm going to ask them and then -- because I think they
12 relate to one another. The first is many of our
13 adulteration standards for food talk about significant
14 and unreasonable risk of illness and injury. So I'm
15 wondering, is there a relationship between the food
16 adulteration standard and your standard for reasonable
17 risk for healthy volunteers.

18 And the second question -- and this
19 sort of gets to what Bob Heflich was talking about
20 later, is do we need to develop information now when
21 we're considering the policy and what you need to
22 collect to make a decision knowing that the ultimate

1 decision is in the hands of informed consent by the
2 patients. That is, does that mean that we need to
3 look at this in a div way than we would for another
4 kind of risk? Say for a prescription drugs where the
5 decision is made by a learned intermediary?

6 DR. KEVIN PROHASKA: I'm going to
7 tackle your first question first. But keep the thing
8 because I want clarification on your second question.

9 The first one as far as the standards
10 that are used within (indiscernible) standard, I've
11 not ever been brought into any conversations within
12 (indiscernible), but I would imagine that the context
13 is quite different as far as food and what's available
14 out in the market. And so the threshold that we might
15 use for what's reasonable, likely to be different in
16 that context I would assume. So as it is, whether
17 you're talking about cancer treatments versus hair
18 loss treatment, the threshold that we use in the drug
19 environment varies depending on the indication.

20 And if you could please clarify the
21 question number two?

22 DR. DAN LEVY: So we have to think

1 about risk as we develop the science behind whether
2 we're going to do this or not. So does the fact that
3 it's going to healthy volunteers who are going to have
4 to give informed consent, does that change the kind of
5 information we need to develop so that the healthy
6 volunteer will be able to give an informed consent?

7 DR. KEVIN PROHASKA: Okay. Fair
8 enough. Well, each division, if you will, there are
9 certain standards of what's expected to be done before
10 going into first in humans (indiscernible). And it
11 may differ by indication and the acuity of the
12 illness. Whether you're going into healthy subjects
13 as a Phase 1 study or people with a condition Phase 1
14 study, there may be some differences as to what's
15 required. I would probably turn to the Review
16 Division and ask for their opinion on that. But at
17 the end of the day, we want to have some basic
18 understanding of the safety profile or at least some
19 understanding of what sort of signals we might need to
20 look for during the Phase 1 studies so that way we can
21 adequately inform the subjects no matter what
22 population it is, whether it's healthy people or

1 people with a condition. And as you go through Phase
2 2 and Phase 3 and so forth, you're learning more and
3 more about the drug. And so the consent document is
4 likely to change considerably.

5 In the Phase 1 environment, I would
6 expect the informed consent document to probably have
7 a lot of open-ended statements about not knowing what
8 the risk profile looks like, but that we think it's
9 this based on whatever. You know? Hopefully that
10 answers your question, sir.

11 MAN: Is there any research to study
12 how well the volunteers understand the information in
13 the informed consent about (indiscernible)?

14 DR. KEVIN PROHASKA: Understanding.
15 Whether or not they understand the consent document, I
16 think that was the question. That's critically
17 important, especially if there are some serious risks.
18 And how well do I think that they understand it? I
19 don't know. But if you look at the literature,
20 frequently you find that people don't understand. And
21 so I think if there are very serious risks,
22 consideration might be given to testing their

1 understanding. And there's one common method for
2 testing the understanding, is the test back. You
3 present the list, perhaps, and you ask people to
4 explain it to you. You know, what did you hear?
5 Please tell me what sort of understanding of the risk.
6 And if they can't explain it within a reasonable way,
7 then maybe you haven't done a good job of explaining
8 what the risks are, and you go back to scratch and
9 explain again that these are the risks, and do you
10 understand and so forth.

11 Does that help? Okay, good. There are
12 other ways (indiscernible).

13 MAN: Do you think there's any
14 difference in the way healthy subjects and patients
15 decide to be in clinical trial? It seems like a
16 healthy subject could decide, well, to avoid this risk
17 completely, all I have to do is not be in the trial,
18 whereas a patient might decide, well, I feel sort of
19 obligated to be in the trial because I have this and
20 maybe I could get (indiscernible) or maybe I could
21 help more?

22 DR. KEVIN PROHASKA: Yeah, very good

1 question. Thank you very much. With people with the
2 condition, a big part of the conversation is not just
3 the risk profile of the drug, but also a discussion
4 about the alternative available therapies. You need
5 to make certain or hopefully make certain that they
6 understand what else is out there, that there are
7 other -- if there are other -- if there are not, then
8 maybe they may not have other options. And again, you
9 have to be careful that they understand the risks, the
10 focus of the research, and so forth and so on.

11 All right. Glad there are questions.

12 WOMAN: I think we have to move on.

13 DR. KEVIN PROHASKA: Okay, fantastic.
14 Thank you very much, everyone.

15 DR. TIMOTHY ROBISON: Our next speaker
16 is Dr. Bob Dorsam. He is in the Office of Generic
17 Drugs. He is the Pharm-tox division director. The
18 title of his presentation is entitled Considerations
19 for a Genotoxic API in Clinical Trials: Healthy
20 Subjects or Patients?

21 DR. BOB DORSAM: Good morning and thank
22 you very much to the organizers, Dr. Tim Robison, Dr.

1 Aisar Atrakchi, for organizing a session a very
2 important topic. Also I'd like to start by thanking
3 in advance our expert panel for providing their
4 insight on what we have, some complex but very good
5 questions.

6 I'm coming to you today as a member of
7 the Pharm-tox discipline. I very much intend today to
8 present a high-level view of what information from a
9 genotoxic perspective we have available at certain
10 points in clinical development. So in part I'll paint
11 a picture of what information we have prior to Phase
12 1, because that's one of the focuses of our talk
13 today, of our session. But then secondly, I'll also
14 present a second frame, which is after that initial
15 approval, there is subsequent applications that are
16 also (indiscernible) to develop similar products,
17 similar API. There may be more information available.
18 And also we are interested in using that more
19 information to the best of its value.

20 My intent is to present two frames, one
21 at the Phase 1, and then secondly paint that portrait
22 of when we're developing generic drugs, for example,

1 what information do we have. And then I'm simply
2 going to pose questions that exist at each of those
3 stages.

4 Okay, so starting at the high level.
5 Clinical trials are integral to support the
6 development of new drug applications, biologics, as
7 well as ANDA submissions. ANDA for those of you who
8 don't know, stands for Abbreviated New Drug
9 Applications. That's a generic drug submission. All
10 of those submission types have trials underneath them.
11 And the safety of clinical trial subjects in all of
12 those submissions is critical. It's a
13 multidisciplinary issue.

14 Now, as pharm-tox, it is assessing the
15 genotoxic risk of the active ingredient. And to
16 support that assessment, we have both invitro and in
17 vivo studies as is described in ICH guidance, ICH
18 S2(R1). And we are assessing this to inform safety in
19 clinical trials. And we have several things going for
20 us, but we also have several -- in terms of
21 standardized studies and information on how to
22 interpret data. But there are also several areas that

1 warrant some further consideration. And that's one of
2 our purposes for coming here today.

3 So clinical trial safety is a complex
4 review issue. There are many different sorts of
5 toxicities that we aim to minimize or mitigate the
6 risk of. Today we're strictly focused on genetic
7 toxicology. Now, as I said, for the protocols for
8 many of the gene-tox studies are standardized. For
9 example, according to OECD protocols. And we have
10 guidance such as S2(R1) and N3(R2), which provide
11 guidance on how we interpret some of these results as
12 well as the timing of their submissions.

13 Okay, so the question that we're here
14 today to question is how do we interpret some of these
15 study results to translate it to safety for clinical
16 trial subjects? And as you've heard before, one of
17 the question is whether to involved healthy subjects
18 in these trials where there are some results to
19 suggest an Ames-positive API, active pharmaceutical
20 ingredient. Should we involve healthy subjects, or
21 rather are patients really the appropriate subjects?

22 Also, as you've heard, there are

1 several mitigation strategies in a trial that also
2 help to ensure safety. And so we look forward to
3 panel's input on how to appropriately mitigate some of
4 the risk using those strategies.

5 So as I mentioned, ICH S2(R1) presents
6 us with a gene-tox battery. And that will inform
7 several mechanisms of gene-tox risk. And if an
8 applicant chooses to take Option 1 in the guidance,
9 they would provide a study which informs invitro
10 mutagenicity or the Ames assay. They would also
11 present in their submission invitro chromosomal damage
12 information. There is also an option to provide
13 mutagenicity in Option 2, study on mutagenicity, as
14 well as an in vivo gene-tox assay.

15 So to put this a little bit more
16 clearly, prior to the IND, we have this Option 1 and 2
17 from ICH S2(R1) that will inform trial subjects in
18 clinical trials. And then as clinical trial
19 development continues, and perhaps that's several
20 years go by, by the time the new drug application is
21 submitted, all of the information from the clinical
22 trials would be submitted for assessment, whether this

1 product is actually safe and effective.

2 And during that long development, there
3 may be follow-up assays and perhaps carcinogenicity
4 studies if in fact they're needed for that
5 (indiscernible).

6 So pharm-tox assessors are really
7 relying on that gen-tox battery from S2(R1) prior to
8 Phase 1 trials and (indiscernible). This is the
9 primary focus of today's talk.

10 Any questions as you've heard remain
11 about how individual results from these studies inform
12 patient or healthy subjects?

13 So let's put ourselves for a moment in
14 the place of a pharm-tox reviewer or a pharm-tox
15 assessor, as we call them. At the IND stage, we have
16 invitro mutagenicity information, we have invitro
17 clastogenicity information. And if we can just
18 imagine a hypothetical compound A, after reviewing the
19 studies, we find that there is a positive signal for
20 mutagenicity and perhaps there is a negative signal
21 for clastogenicity.

22 So at that point a pharm-tox reviewer

1 is faced with a question. And the quandary that
2 they're in has been from (indiscernible). But one of
3 the questions that we have is if a drug is genotoxic,
4 and in this case mutagenic, is there a follow-up study
5 to assess potential risk that should be done prior to
6 conducting studies in healthy subjects? So the
7 appropriate follow-up is a question.

8 Secondly -- and this is a little bit
9 aside the primary focus of the session today. But if
10 we look at compound B, we have a compound that's
11 negative for mutagenicity but positive for
12 clastogenicity. Okay? So again, a little bit
13 different from the primary focus. When accepting
14 questions from various people in preparation for this
15 session, one of the questions was for a case like
16 this, certain drugs may be clastogenic but mutagenic.
17 Should consideration be given to the mechanism of
18 action of gene toxicity in designing studies with
19 healthy subjects? So effectively does it matter if
20 it's mutagenic or clastogenic? Should they be
21 considered similarly? This is a lasting issue that
22 came up in preparation. So we thought we would pose

1 that to the expert panel as well.

2 As Dr. Robison mentioned, there is
3 considerations on trial design. So does it matter if
4 a healthy volunteer is exposed up to a single dose or
5 up to four doses of an active ingredient? And I'll
6 speak in a moment about why four doses of an active
7 ingredient is notable or why I picked four.

8 In most cases is continuous daily
9 dosing acceptable, and if so, for how long? Or
10 otherwise, is intermittent dosing preferable, and if
11 so, how many doses would be acceptable in those cases?

12 So dosing in clinical trials can take
13 many different forms. The does level, the frequency
14 of dosing, and the dosing interval could all be
15 adjusted for safety. And certainly those are
16 considerations that we pose to the expert panel for
17 consideration and providing our feedback.

18 I'm providing one example of a typical
19 clinical trial. So in this case, it's called a single
20 dose two-way crossover trial design. This is a case
21 where some test product is looking to establish a
22 bridge to a reference product. So to establish that

1 bridge, they're going to dose test article and the
2 reference product in a patient or in a healthy
3 volunteer and establish some similarity between
4 pharmacokinetic characteristics. Okay?

5 The two-way aspect of it is if you have
6 the test dose followed by washout and then reference -
7 - so that would be A and then B, we would then later
8 have B, then A. Again, comparing the pharmacokinetic
9 (indiscernible) to establish similarity. So the
10 question is, does it matter if a healthy volunteer is
11 exposed to a single dose for up to four doses?

12 And as we've seen and heard,
13 microdosing is of course another consideration. As
14 we've heard, it's used relatively rarely. But
15 altering the dose may be one option. In M3(R2) we see
16 that a dose of 100 micrograms is reasonable, or up to
17 five of these doses may be used at a microdose trial
18 if that suits clinical development.

19 So that's at the IND stage where we
20 have mutagenicity and clastogenicity. One of the
21 things that I would like to show you today is that
22 later in the lifecycle there are applications, namely

1 505(b)(2) and 505(j). 505(j) is a generic drug
2 solution. And these applications often are looking to
3 bridge back to the safety and efficacy of an original
4 submission. Okay? So a 505(b)(2) may rely on some
5 information that the applicant doesn't know and maybe
6 something that was published, it may be a more
7 abbreviated clinical development program, as a generic
8 drug is aiming to establish prior equivalence. Okay?
9 So they're not showing safety and efficacy; they're
10 really showing prior equivalence to what we call the
11 reference listed drug, or the innovator product.
12 Okay? So therein a pharmacokinetic bridge is pivotal
13 to their drug development program.

14 Now, the benefit that we have in these
15 sorts of applications is that the genetic toxicology
16 and carcinogenicity information are stated in the
17 drugs labels that's been approved. So that's a bonus.
18 However, we do need clinical trials in these
19 application types to develop those drugs. So we have
20 more information. There is a need to develop these
21 drugs. Questions still remain about a way to resolve
22 all of these studies for clinical trials supporting

1 these applications.

2 And so we too are faced on the generic
3 side with the question of should we involve patients
4 or healthy subjects in these trials and should we
5 adopt certain risk mitigation strategies to protect
6 their safety?

7 I say this because a large number of
8 505(b)(2) applications, as well as generic drug
9 applications are submitted to CDER. Ninety percent of
10 prescriptions are generic drugs. And we certainly
11 want to ensure that the trials that are supporting
12 them involve similar sorts of safety principles so
13 that subjects in those trials are not put at greater
14 risk than those of the original innovator application.

15 So I've told you (indiscernible)
16 generic drugs. We do have more information. When
17 generic drug has a clinical trial, okay, they need to
18 demonstrate bioequivalence to the reference-listed
19 drug. And that will involve either healthy subjects
20 or patients. So input from today's session is very
21 much important to me in this regard.

22 To demonstrate bioequivalence, they'll

1 dose a test article, a dose of reference product.
2 There will be a trial under fasting conditions, a
3 trial under fed conditions to ensure that there is
4 similar bioequivalence across both conditions.

5 And a safety review is done to consider
6 prior use of healthy subjects in the innovative
7 program. So currently generics are using healthy
8 volunteers when, for example, healthy volunteers have
9 been used in the past.

10 Also in collaboration with our
11 colleagues from the Office of New Drugs, Office of
12 Generic Drugs folks are sometimes reaching out to
13 ensure that healthy subjects (indiscernible) for this
14 trial for generics.

15 But I do note that genetic toxicology
16 information and carcinogenicity information have been
17 reviewed, it's in the (indiscernible) label, and we're
18 looking to use that information to its greatest value
19 to inform this healthy or patients topic. And we
20 certainly look to the expert panel for some assistance
21 in how to weigh this information. And I say that
22 because we surveyed FDA-approved drugs labels for APIs

1 that have positive results in gene-tox or
2 carcinogenicity studies.

3 Within our team, we've used a tool
4 called FDA Label. Now, FDA Label is developed by our
5 colleagues in NCTR. FDA Label draws from the
6 structured product label resource. And there are
7 about 35,000 prescription drug labels in this archive.
8 We merely did a keyword search for the non-clinical
9 section of drug labels using the term positive.
10 Because oftentimes when a new study is positive,
11 that's the way it's going to be on the drug label. So
12 we just search all of the available labels for the
13 word positive in this one section of the label. And
14 out of the 35,000 or so labels, you'll get about 3,200
15 results. But there are many duplicate applications
16 and many duplicate drug labels. So if you remove all
17 duplicates, you've still kind of got 250 non-duplicate
18 APIs that have the word positive in the drug label.
19 And we just took a subset of that. We took about 30
20 applications, 30 drug labels, and then just calculated
21 what the results are.

22 My goal is not to show you the results

1 here, but merely to say when looking at those results,
2 it does stand out that some APIs have a positive
3 result in either neutral or in vivo assays. And there
4 are APIs and antivirals, antihypertensives. There are
5 some therapies for migraine, acid reflux, high
6 cholesterol, arrhythmia, or inflammation. There are
7 positives from individual assays.

8 What we want to do is use this
9 information to the best of its abilities so that trial
10 subjects for these studies are put at no greater risk
11 than in other trials. So we have more info.

12 And our question is, now what? So if
13 we go back to that Compound A that is positive for
14 mutagenicity, later on after the drug was approved, we
15 find out that it's negative for carcinogenicity. So
16 perhaps we can (indiscernible) perhaps maybe healthy
17 volunteers may not be a problem. Perhaps the positive
18 clastogen also shows to be positive in
19 carcinogenicity. Okay? So either of these compounds
20 are anonymized, but there are examples that fit into
21 this sort of a case. So these could be said in, you
22 know, real cases.

1 My question to the panel is should a
2 weighted evidence approach be used to decide whether a
3 compound should be tested in bioequivalence studies
4 with healthy subjects. If yes, which test results
5 should receive the greatest consideration in the
6 weight of evidence assessment? Also, are there any
7 other factors relating to genetic toxicology that
8 should be considered when determining if a study
9 should include healthy subjects in these
10 bioequivalence studies?

11 So what I've done is gone over somewhat
12 quickly some of the questions that the panel will be
13 encountering later in the afternoon. My hope is that
14 I've provided some look at the sort of data that was
15 presented to our pharm-tox assessors at the Phase 1
16 stage. But also later on when trials are being
17 conducted for 505(b)(2) as well as generics.

18 The questions that we pose are
19 regarding dosing, and specifically how many doses of a
20 positive drug can be safely administered to healthy
21 subjects. Is it one, two, three, or four doses? Is
22 continuous dosing acceptable? So for how long? Or

1 rather if the dosing is intermittent, how many doses
2 would be acceptable? These are questions that are
3 remaining for us.

4 Secondly, we've heard a question about
5 follow-up assays. Are there appropriate follow-up
6 studies that should be conducted prior to studies in
7 healthy volunteers if an API is Ames-positive? We
8 also pose a question regarding mechanism. Certain
9 drugs may be clastogenic, but not mutagenic. Should
10 consideration be given to the mechanism of actual
11 genotoxicity and designating studies with healthy
12 volunteers?

13 And then a question about weight of
14 evidence. Should a weight of evidence approach be
15 used to decide whether a compound should be tested in
16 bioequivalent studies with healthy subjects? If yes,
17 which studies should we give the greatest
18 consideration to, and then are there any other factors
19 that we should consider when doing this assessment?

20 So with that I'll just finish with a
21 quick summary of saying clinical trial safety is of
22 paramount importance and genotoxic risk is very much

1 important and underlying some of the safety that we
2 wish to uphold for our trial subjects. We have
3 different information prior to first in human studies.
4 We have more information available at later stages
5 when clinical trials are also conducted.

6 Our question, healthy subjects with
7 patients is a key consideration for risk management
8 for (indiscernible), biologics, as well as for the
9 generic drug applications.

10 Not only healthy subjects or patients
11 are a consideration, but also those trial design
12 elements that might make a risk. And you can
13 certainly appreciate the expert panel's insight on how
14 to best translate available information and the
15 appropriate safety recommendations for participants in
16 these clinical trials.

17 With that I'll just briefly acknowledge
18 my colleagues in the Office of Generic Drugs who
19 assisted me in the formation of the slides, as well as
20 the FDA Label exercise that we went through. My
21 collaborators in the Office of New Drugs who were
22 helpful in also creating the slides, as well as

1 formulating the questions that we are posing here
2 today. And my colleagues at NCTR who developed a
3 great tool to get information within FDA labels in a
4 way that I think is pretty unique and pretty powerful.
5 So with that, I'll say thank you. And happy to answer
6 any questions.

7 DR. TIMOHY ROBISON: We have time for
8 one quick question.

9 MAN: So in your slides, you mentioned
10 about geno-tox, and you mentioned (indiscernible).
11 But to my knowledge, none of the standard battery
12 actually (indiscernible). So, I mean, are you
13 recommending we recommend screening with
14 (indiscernible)? And for drugs that we said no
15 pharmacology on the genetic regulation, do we consider
16 actually patients instead of healthy volunteers in
17 Phase 1 study?

18 DR. BOB DORSAM: Thank you for a very
19 good question. So I'm not proposing necessarily that
20 there should be something added to the standard
21 battery. I'll leave that to my colleagues who are on
22 the ICH S2 to consider whether to expand the battery.

1 The question is good. Where there is a named
2 pharmacologic effect towards (indiscernible), I think
3 that that is an important consideration. That
4 question will be addressed a little bit more so with
5 some slides and further discussion this afternoon by
6 the expert panel. So I think you raised a good
7 question, and it's one that I think we're going to
8 (indiscernible) a little bit later. Okay, thank you.

9 DR. TIMOTHY ROBISON: Mike, I was just
10 asked to announce that people can please mute their
11 phones. And when you're speaking into the microphone
12 to speak -- to identify yourself and speak clearly.

13 Our next talk, Doctors Petibone and
14 Shemansky, spent over a year investigating the
15 literature in terms of exposure to a small number of
16 doses of a genotoxic drug and the potential health
17 risks. Dr. Petibone is here today to present the
18 results of this literature review. Thank you.

19 DR. DAYTON PETIBONE: Thank you.
20 Great, thanks. So yes, in order to prepare for this
21 event, we have conducted a review of the literature to
22 identify studies that could inform the risks

1 associated with administering one or a few doses of
2 DNA-reactive drugs, particularly Ames-positive drugs,
3 to help these subjects during Phase 1 clinical trials.

4 So here are presented some of the most
5 informative findings from this ongoing effort. So the
6 approach to this was fairly simple. We reviewed basic
7 databases and search engines such as PubMed, Google
8 Scholar, and the (indiscernible), as well as some
9 other search engines and database to a lesser extent.

10 The search terms that were queried
11 concerned the mutagenicity and related search terms to
12 that and the Ames test, as well as exposures that were
13 at milligram doses, which is the dose range in which
14 APIs would be administered to healthy subjects during
15 Phase 1 clinical trials.

16 We also looked for exposures that were
17 done in animal model studies as well as reviewing the
18 literature for any data that were present for
19 exposures in human subjects with cancer endpoints.

20 We looked for data modeling of the
21 threshold of toxological concern and the threshold of
22 regulation for modeling of less than lifetime

1 exposures, and then we looked at a number of different
2 dose levels.

3 So today we've summarized the findings
4 from over a hundred relevant and supporting documents
5 and subject areas such as data modeling and database
6 analysis, animal studies with single, few, or short
7 duration exposures to DNA-reactive endpoints that also
8 had -- or DNA-reactive agents that also had tumor
9 endpoints. And cancer epidemiology studies for
10 environmental, occupational, and medical exposures to
11 DNA-reactive agents.

12 In addition to that, we've compiled
13 over 1,300 manuscripts that contain single exposures
14 to test articles in animal models that have tumor
15 endpoints.

16 So to ask the question, can we use the
17 existing data to assess the risk of administering an
18 Ames-positive drug to healthy subjects during Phase 1
19 clinical trials, I have chosen two subject areas to
20 review. And that's the data modeling and database
21 analysis of Ames-positive chemicals. And also the
22 second section deals with cancer data from single,

1 few, or short duration exposures to Ames-positive
2 chemicals in animal models and in humans.

3 So for Part 1, the first study, I've
4 chosen to analyze the EPA GENE-TOX database to provide
5 an assessment of the Ames assay's ability to predict
6 carcinogenesis. The second study that we looked at
7 reviewed the NTP Database for studies with short-term
8 exposures as well as chronic lifetime exposures to see
9 if the chronic exposures could predict the
10 carcinogenic effects of the short-term exposures.

11 So because chemical-induced
12 carcinogenesis can often involve both genotoxic and
13 non-genotoxic events, it's difficult to predict how
14 well a specific gene-tox assay would predict its
15 carcinogenic potential. So a retrospective study was
16 performed of the EPA GENE-TOX Database of over 3,500
17 chemicals with GENE-TOX data. Of those, over 1,600
18 had Ames-positive data, and 988 of those also had
19 rodent cancer bioassay data.

20 So the investigators in this study,
21 Matthews and colleagues, sorted the data according to
22 their outcomes of the Ames assay, whether those were

1 positive or negative. And they then classified those
2 events by their findings in the rodent cancer
3 bioassay. So in this instance, there are 275
4 chemicals that were positive for both mutagenicity and
5 for carcinogenicity, as well as 282 chemicals that
6 were positive for carcinogenicity, but negative for
7 the mutagenicity. And then for the compounds, they
8 were negative for carcinogenicity. There were 85 that
9 were positive for mutagenicity in the Ames assay as
10 well as 346 that were negative for both
11 carcinogenicity and mutagenicity.

12 So when they evaluated the Ames assay
13 for its ability to predict carcinogenicity, they
14 looked at the causative predictive value. And for the
15 Ames assay there was a 76.4 percent prediction that --
16 predictability to identify the fraction of mutants
17 which are carcinogens. And then for the specificity,
18 there was a 80.3 percent ability to identify the
19 fraction of non-carcinogens which are not mutagens.
20 So they also looked at a correlation indicator which
21 is an indicator of a positive finding of an aerobic
22 cancer bioassay. And they found good agreement with

1 the Ames assay and the ability to predict
2 carcinogenesis with a 78.3 percent return on that. So
3 this indicates that the Ames test is a reliable
4 indicator of a positive finding of the aerobic cancer
5 bioassay.

6 Next we looked at a study that
7 evaluated chronic lifetime exposures as well as stop
8 exposures. Stop exposures refer to studies in rodents
9 which are initiated and then terminated several months
10 following exposure.

11 So cancer risk assessments assume that
12 excess risk increase as a linear function of a
13 cumulative carcinogen dose administered at a given
14 rate, also known as Haber's Law. So for instance,
15 Haber's Law would predict that an exposure for two
16 years to a carcinogen would pose one-tenth of the risk
17 of an exposure for 20 years to a carcinogen.

18 So to test this assumption, 11
19 carcinogens were identified in the NTP Database that
20 had both combined lifetime and stop exposure data.
21 The data were then modeled to determine the maximum
22 likelihood that corresponded to a one percent increase

1 in cancer risk.

2 So it was identified that tumor
3 incidence was significantly higher for six of 11
4 chemicals in this database, the 11 chemicals that are
5 shown in the table to the left here. And one thing
6 that most of them have in common are that five of the
7 six are positive for findings in the Ames test. So
8 ADBAQ and ortho nitro anisole were positive in two
9 Ames assays. And then BBMP, 1,3-Butadiene, and
10 coumarin were positive in at least one Ames assay.
11 Methyl eugenol was the only carcinogen that produced a
12 positive response that was negative for the Ames
13 assay.

14 So what they found was that most of the
15 carcinogens in the stop exposure studies had
16 significantly higher -- a greater than twofold
17 response in cancer potencies than the chronic lifetime
18 exposures for at least one tumor site.

19 So as an example, in addition to having
20 a twofold greater response, BBMP and 1,3-Butadiene and
21 ortho nitro anisole were positive for increased tumors
22 (indiscernible) only when the stop exposure data were

1 included.

2 The findings from the stop exposure
3 modeling suggest that the short-term exposures could
4 pose cancer risks not identified in a continuous
5 exposure studies. An example of that is 1,3-butadiene
6 exposures for 13, 26, 40, or 52 weeks produced a much
7 higher tumor response in heart hemangiomas as
8 compared with the continuous lifetime exposures for
9 the same dosing rate.

10 So to summarize the findings of Part 1,
11 the GENE-TOX Database analysis suggests that the Ames
12 test is a reliable indicator of positive finding in
13 rodent carcinogenicity bioassays for a mutagenetic
14 agent. The majority, five out of six chemicals in
15 stop exposure studies gave a greater than twofold
16 response in cancer potencies. Were also positive in
17 at least one Ames mutagenicity assay. And also the
18 findings from the stop exposure modeling suggests that
19 short-term exposures could pose cancer risks not
20 identified in the continuous exposure studies.

21 So in the second part we looked at
22 exposures to a single, few, or short duration of

1 exposure to Ames-Positive chemicals. The data that I
2 will go over today are the Single Exposure Carcinogen
3 Database, which is an accumulation of animal studies
4 that have a single exposure to a chemical. And then I
5 will go over some examples of epidemiological data
6 where subjects were either exposed occupationally or
7 to a medical exposure for a short time. And a short
8 duration in this context refers to a time less than or
9 up to a year.

10 So the chemicals for the occupational
11 exposures are beryllium, which are in a wide range of
12 products. And the cohort are the beryllium production
13 workers. We then looked at the aromatic amine
14 benzamidine and the cohort of workers involved in the
15 manufacture, use, and purification of those compounds.

16 For the medical exposures, we looked at
17 phenacetin, which is an OTC analgesic. Its use was
18 discontinued in the U.S., Canada, and the U.K.
19 Chloral Hydrate, which is a prescription sleep aid,
20 and then finally we looked at Thorotrast, which is a
21 contrasting agent. It's a little different from the
22 other exposures, because it is an alpha-emitting

1 particle. And it was used from the 1920s until it was
2 discontinued in the 1950s.

3 So as it turns out, there are numerous
4 studies that have data for a single exposure in animal
5 models. And these have been compiled by Calabrese and
6 Blain into a database of tumor incidence following a
7 single exposure in order to estimate the less than
8 lifetime exposures. This database contains over 5,500
9 studies for 800 chemicals from 2,000 articles that
10 address the single exposure carcinogenesis.

11 So in order to be included in the
12 database, the agent could be administered only once
13 with no other treatments administered. And the tumors
14 were examined as the endpoint. The database compiles
15 a number of metrics such as; the number of citations
16 each study has accumulated; chemical details such as
17 the (indiscernible) number, synonyms, and chemical
18 class; the study design, which includes the controls,
19 treatment groups; and other principal aspects of those
20 studies.

21 So as Tim mentioned earlier, there are
22 426 chemicals with doses that were administered as a

1 single dose. And those spread across 17 chemical
2 classes, with many of those containing mutagenic
3 compounds such as polyaromatic hydrocarbons,
4 nitrosamines, hydrazine, and nitrosourea classes.

5 When we do a comparison of the studies
6 that were positive for tumor induction as well as
7 those that were negative for tumor induction, there
8 were over 4,200 studies that were positive for tumor
9 induction following the single exposure to a chemical,
10 as well as nearly 1,300 studies that were negative for
11 induction of tumors following exposure to the
12 chemicals.

13 So both the studies that were positive
14 and the studies that were negative were similar in
15 several key aspects, some of their principal aspects.
16 For instance, the studies that were positive and were
17 negative, both used a similar percentage of both male
18 and female sexes and incorporated both sexes into
19 those studies. In addition, both positive and
20 negative studies used histology as a endpoint.

21 They also were similar in their number
22 of subjects per group in that a number of them used

1 ten or more subjects per treatment group, and a
2 similar percentage of them also used greater than 50
3 subjects per treatment group. They also varied
4 somewhat in some of the principal aspects of their
5 study design, such as mammary tissues being looked at
6 as an endpoint for tumors and respiratory tissues.

7 In addition, the studies that were
8 positive used a higher percentage of rats as compared
9 to the studies that were negative. And those studies
10 that were positive particularly used the Sprague
11 Dawley rat, which might explain some of the positive
12 findings in the mammary tumors. And the studies that
13 were negative used a larger percentage of mice.

14 So what the study found was that a
15 single dose of many agents produced tumors in both
16 males and females and in all age groups, whether it
17 was fetal, neonate, or adult stages. And the findings
18 were positive in numerous animal models. You can see
19 the table on the left that there is a diverse set of
20 species that were positive following a single exposure
21 to a chemical.

22 The doses that resulted in tumors were

1 generally low proportion of the LD50, between 0.1 and
2 up to the LD50 itself, and not acutely life-
3 threatening. The tumorigenic responses observed for a
4 single exposure to the DNA-reactive chemicals had wide
5 structural diversity and were in all principal animal
6 models and several other animal models, implies that
7 humans are likely to exhibit qualitatively similar
8 responses.

9 Next, they look at a single dose versus
10 a fractionated dose. So the single dose was
11 administered once and the fractionated dose was
12 administered over the lifetime of the animal for an
13 equal and cumulative dose.

14 So when they compared the single dose
15 and the fractionated dose, they found that there were
16 some chemicals where the single dose caused fewer
17 tumors than the fractionated dose. That's shown on
18 the left here.

19 There are also chemicals where a single
20 dose caused more tumors than the fractionated dose for
21 a given tumor site. And then there were chemicals
22 where the single dose and the fractionated dose

1 produced similar results in tumor response.

2 Also, some of the chemicals produced a
3 mixed result, such as DMBA, benzoate pyrene, 3-Hydroxy
4 xanthine and procarbazine, where depending on the
5 tumor sites, they were either fewer tumors, more
6 tumors, or an equivalent number of tumors produced in
7 both the single and the fractionated dose. So this
8 suggests that there are chemical-specific carcinogenic
9 responses or varied responses to a single versus
10 fractionated dose and that the single dose can have
11 carcinogenic effects that aren't always observed in
12 lifetime exposures.

13 So because cancer epidemiology studies
14 usually address the results of prolonged exposures,
15 the short duration exposures or single exposures to a
16 carcinogenic compound can sometimes be overlooked.
17 And it is also difficult to associate an exposure
18 event that might have happened 20 or more years ago
19 with cancer. Therefore, there are limited data for
20 DNA-reactive or mutagenic exposures in humans.

21 For the analysis of exposure in humans,
22 we considered a short duration exposure to be that of

1 less than one year or exposures to one or a few doses.
2 And human subjects exclude those that have cancer or
3 terminally ill patients. And the treatment includes
4 drugs or chemicals with positive mutagenicity data and
5 exclude antineoplastic drugs.

6 So for short duration occupational
7 exposures, we looked at beryllium and the aromatic
8 amine benzidine. Beryllium was negative in the Ames
9 assay, but it was positive for HPRT mutations in CHO
10 cells and in Chinese Hamster B79 cells. The cohorts
11 that were investigated were white males that entered
12 into the beryllium case registry and that were
13 involved in the manufacturing of beryllium.

14 So what the investigators of these
15 studies found is that employment of a year or less to
16 beryllium resulted in significant increases in the
17 incidence of lung cancer.

18 Then for the aromatic amines benzidine,
19 the subjects that were involved in this study were
20 involved in manufactured use and purification of the
21 AABs. What this study found is that the overall risk
22 from dying from a bladder tumor is approximately 30

1 times greater than that of the general population if
2 exposed for at least six months and exposed up to one
3 year.

4 The table shows the findings of the
5 short duration occupational exposure of beryllium in
6 humans. So there are seven cases of lung cancer that
7 were reported. All reported acute chemical bronchitis
8 upon entry into the beryllium case registry. They
9 were primarily involved in the extraction and smelting
10 of beryllium. And of the seven cases, five of those
11 had exposures that were for less than one year. Three
12 workers had exposures for one month, one worker had an
13 exposure for two months. And then there was another
14 worker with an exposure for six months.

15 In a similar study, there were two lung
16 cancer deaths reported 20 years after their last
17 exposure. One was employed for six months and the
18 other was employed for 21 months, which is longer than
19 a year. So the data on smoking history was not
20 collected as part of either one of these studies.

21 So then we looked at short duration
22 exposures to the aromatic amines benzidine. This

1 table shows the different chemical classes that were
2 investigated. Benzidine, alpha-Naphthylamine, beta-
3 naphthylamine, and then mixed exposures.

4 What the table shows is the percentage
5 of the observed number of bladder tumors as compared
6 to the expected number of bladder tumors. And then
7 measured the effect of time and the incidence of
8 cancer risk.

9 So we can see even with one year for
10 benzidine, beta-naphthylamine, and for mixed
11 exposures, there are increased risk for development of
12 bladder cancer. And you can see that that increases
13 for those same chemical classes up to one year and
14 that with increasing time there is an increasing risk
15 for developing bladder cancer before that risk drops
16 off at 20 years.

17 But all of the subjects that went into
18 these data developed tumors. So after developing
19 tumors, they were removed from the study, which
20 explains the shape of these data in the graph.

21 So what they found was that even with
22 less than a year exposure, that there were increased

1 risk for developing bladder cancer. And also, again,
2 as I note, the data for smoking history was not
3 collected as part of this study.

4 So we then went to look at short
5 duration medical exposures. Phenacetin, which was an
6 OTC analgesic, had mixed results in the Ames test and
7 was positive only in the presence of S9. It also was
8 positive for (indiscernible) mutations in the kidneys
9 of transgenic rodents. The dosage of phenacetin is
10 generally 300 milligrams four to six times a day and
11 not to exceed two grams.

12 One study by Ross and colleagues looked
13 at the consecutive or continuous use of phenacetin and
14 compared that to less frequent use of -- less than 30
15 days a year -- or greater than 30 days a year, less
16 than 30 days a year, or no use. Chloralhydrate is a
17 sleep aid and it has mixed results in the Ames assay.
18 It's generally prescribed as a 500 milligram dose.
19 And Haselkorn and colleagues looked at the effect of
20 zero, one, two, three, of four doses of chloralhydrate
21 and the incidence of cancer over a four-year period.

22 And then finally we looked at

1 thorotrast, which is positive for T-cell receptor
2 mutations. It's negative for GPA mutations and had
3 mixed results in the p53 and KRAS gene mutations
4 assays. There were no data for the Ames assay for
5 thorotrast.

6 So there have been over 9,000 people
7 injected with thorotrast between 1929 and 1956. It's
8 generally administered acutely at a rate of 500 grams
9 per liter and volumes that can range from one mL all
10 the way up to 100 mLs. The study we looked at today
11 observed that there were dose-dependent increases in
12 the time to tumor formation with increasing volume of
13 the thorotrast that was injected.

14 So phenacetin is classified as a Group
15 1 carcinogen, carcinogenic to humans. And it was
16 withdrawn from the U.S. market in 1983. The long-term
17 use of phenacetin has been shown to cause renal and
18 ureter tumors in humans. And in a study by Ross and
19 colleagues, they looked at men and women from the Los
20 Angeles Case Registry and with the matching controls
21 for those cases. The doses of phenacetin that were
22 used were continuous exposure for more than 30

1 consecutive days in a year or use of phenacetin for
2 more than 30 days per year. And then those were
3 compared to use of phenacetin for less than 30 days
4 per year or no use. They calculated the
5 (indiscernible) of phenacetin use and then adjusted
6 that to the controls that were either no use or fewer
7 than 30 times per year.

8 And what they found was that there was
9 a slight yet nonsignificant increase in the risk for
10 renal, pelvis, or ureter tumors in those that had 30
11 days of consecutive use as compared to those that were
12 either greater than 30 days per year or less than 30
13 days per year or that had no use of phenacetin. So
14 this shows that some risk was involved with exposures
15 to a carcinogen with continuous use.

16 Next we looked at short duration
17 chloralhydrate administration. So chloralhydrate is a
18 mutagen in salmonella that was positive in four out of
19 six assays using TA100 and was positive for two assays
20 using TA104 strains. It was also carcinogenetic in
21 animal studies. And chloralhydrate is a major
22 metabolite of trichloroethylene, a general anesthetic

1 that was banned in the U.S. in 1987 due to its ability
2 to induce tumors in rodents.

3 So Chloralhydrate was used in a 500
4 milligram form, or dispensing as it's referred to it
5 in the paper. Based on the study, most patients
6 received a few doses of 500 milligrams for short-time
7 use.

8 When they analyzed the data -- so the
9 table on the left shows the number of cases that
10 developed a cancer versus the other chloralhydrate
11 users that did not develop cancers that were used to
12 calculate the dose response. And what they found is
13 that for all cancers overall, there was no significant
14 increase and no dose response. However, when they
15 looked at prostate cancer, they found that there was a
16 dose response for induction of prostate cancer with
17 increasing numbers of chloralhydrate doses, from three
18 cases for one dose, five cases for two to three doses,
19 and six cases for four or more doses. So this
20 suggests an increased risk of prostate cancer with the
21 increasing number of doses that were administered.

22 So finally, the last chemical we looked

1 at for medical exposure in humans was that of
2 thorotrast. And as I mentioned previously, it is a
3 bit different because it an alpha-emitting agent.
4 thorotrast contains thorium, which has a half-life of
5 ten to the tenth years, and it has a biological half-
6 life of 20 years. So once exposed, the subject is
7 internally exposed to the thorium for the remainder of
8 their life. It's typically used for cerebral
9 angiographies to identify arterial venous
10 malformations or to evaluate head injuries.

11 So the graph on the left shows the
12 cumulative frequencies of liver tumors with time after
13 angiography in relation to the volume of thorotrast
14 that was injected. And the graph on the right shows
15 the cumulative frequency of hematopoietic malignancies
16 amongst subjects injected with thorotrast. And in
17 most of these, you can see that there is a dose-
18 dependent response in the formation of liver tumors
19 that correspond to the dose level that was injected.
20 So the subjects that were injected with 20 mLs or more
21 developed tumors more rapidly than subjects that were
22 injected with 11 to 20 mLs or those that were injected

1 with one to ten mLs.

2 A similar pattern is seen for the
3 development of hematopoietic malignancies. And the
4 subjects that were injected with greater than 19.7 mLs
5 developed the malignancies sooner than subjects that
6 were injected with less than 17 mls as compared to
7 those of the control. So there is an increasing risk
8 -- there was an increasing risk for cancer based on
9 the level of exposure to the mutagenic thorotrast
10 injection.

11 So in summary for Part 2 of the talk,
12 the tumorigenic responses observed for a single
13 exposure to carcinogens with wide structural diversity
14 in all principal animal models imply that humans are
15 also likely to exhibit quantitatively similar results.
16 The cancer epidemiology studies provide suggestive but
17 not conclusive evidence of a causal relationship
18 between short duration exposures to mutagenic
19 compounds and cancer. And of course the examples that
20 I showed you based on the limited data available
21 obviously have their shortcomings and limitations, but
22 they do provide some suggestive data.

1 And finally, as a (indiscernible) that
2 animal experiments have limited exposures other than
3 that of the doses that they are administered, whereas
4 humans are exposed to additional and environmental
5 exposures.

6 So this is an ongoing effort and we are
7 continuing to search the literature to find relevant
8 information as well as we are attempting to
9 reconstruct the Single Exposure Carcinogen Database,
10 exposures that were done in animal models. So I'll
11 take any questions that you have now.

12 MAN: Do we have time for a few
13 questions?

14 DR. ERROL ZEIGER: Errol Zeiger, a
15 member of the panel. You showed that compilation of
16 Calabrese and Blain, which is very interesting. But
17 the problem is they failed to stratify by exposure
18 route. I know back in the old days, in the 1960s and
19 50s, there were a lot of cancer experiments done with
20 single subcutaneous injections or intratracheal
21 injections, which are clearly not relevant to anything
22 that we're talking about now. And without removing

1 these, you'd get a very biased view of it.

2 And I found that the study with
3 (indiscernible) is very interesting. Beta-
4 naphthylamine seems to be -- alpha-naphthylamine seems
5 to be the most potent carcinogen. And it's beta-
6 naphthylamine that's classified as a carcinogen.
7 Alpha is really -- it's not mutagenic, pure alpha.
8 And it's considered to be non-carcinogenic. But those
9 results show just the opposite.

10 DR. DAYTON PETIBONE: I'm looking at
11 the --

12 DR. ERROL ZEIGER: No, I'm sorry. No,
13 the alpha showed the higher response, but the beta is
14 considered to be the carcinogen.

15 DR. DAYTON PETIBONE: Early on, the
16 beta-naphthylamine showed a larger response, it's the
17 open column here, with increasing time. But as these
18 subjects developed cancer, bladder tumors, they are
19 removed from the study so that the remaining studies --
20 -- the remaining tumors that were developed in the time
21 after five years or ten years exposure, it does appear
22 that the alpha-naphthylamine did result in an increase

1 in (indiscernible). But I'm not sure the explanation
2 for that.

3 DR. CHARLES THOMPSON: Charles
4 Thompson, CDER. Excuse me if you've touched on this,
5 I missed it. But I'm curious, what's your single
6 animal exposure database that you looked at? Did any
7 of that involve initiation-type, promotion-type
8 modeling?

9 DR. DAYTON PETIBONE: I would note the
10 only data that we were able to look at was a high-
11 level overview of that database. We were not able to
12 access that database. We are in the process of trying
13 to reconstruct it. That's the 1,300 papers that we
14 have with the single exposure. So we have not been
15 able to do any detailed research into that other than
16 we have gone in and randomly spot-checked some of the
17 studies to see that -- to verify that the findings do
18 match up with those that were found or reported in the
19 Single Exposure Carcinogen Database. But hopefully
20 reconstructing the Single Exposure Carcinogen Database
21 is something that people will think is worthwhile. As
22 of 1999, there were over 2,000 studies that had single

1 exposures in animals in the past 20 years that could
2 have increased quite significantly. And we'd like to
3 compile those data for analysis.

4 DR. PETER CULLINS: (indiscernible)
5 Peter Cullins, London. I think it's really
6 interesting to reconstruct that database. But in
7 doing that, I think we would need to look carefully at
8 at least two aspects. One is the age of
9 administration. Because all of those studies were
10 done by (indiscernible), which I think adds an
11 additional biological component, which is the safe
12 rate of cell replication, which would be different
13 from an adult exposure.

14 And the second is -- and you touched on
15 the thorostrast -- is the difference between a
16 bioaccumulate compound, which although it's a single
17 (indiscernible), it's continuous internal exposure and
18 something which is short-lived but there is a
19 toxicodynamic component. And certainly for the
20 inorganics there will be a significant number of them
21 where bio persistence is a factor.

22 MAN: (indiscernible), CDER. So

1 subjects who are taking from this to be
2 (indiscernible), is there any follow-up?

3 DR. DAYTON PETIBONE: For the short
4 duration exposure to aromatic amines benzidine? I am
5 not sure if there was any follow-up that was conducted
6 with those subjects. It wasn't reported in that
7 study.

8 DR. ROBERT HEFLICH: Bob Heflich from
9 NCTR. (indiscernible) of business that he analyzed.
10 I did happen to read the Calabrese paper yesterday. I
11 looked at it. I was surprised at the few studies that
12 (indiscernible) on the bioassay studies. It was less
13 than 20 percent I believe. And if you look at the
14 (indiscernible), obviously there's a lot of Sprague
15 Dawley model treatment that produced mammary tumor
16 results. But it's not exclusive. I mean, there's a
17 lot more going on there. And I think one of the
18 criteria for inclusion in that database that there
19 were no other treatments other than the single dose.

20 DR. DAYTON PETIBONE: Correct, yes.

21 DR. ROBERT HEFLICH: So there was no
22 promotion (indiscernible) initiation kind of study.

1 AUDIENCE: Just a comment on the
2 beryllium workers. There is also a type of an immune
3 component to beryllium disease. It's almost like a
4 type of allergy that develops. And that also
5 continues to (indiscernible). So it's not just a
6 simple straightforward story and it was
7 (indiscernible), but it's something that
8 (indiscernible).

9 DR. TIMOTHY ROBISON: We scheduled a
10 15-minute break. I think the speakers will be around
11 if you have questions during the break.

12 (Break)

13 DR. DOUGLAS BRASH: Okay. So, first
14 question is, can people in the back row can hear me?
15 And Dan, hopefully, people out in cyberspace can hear
16 you.

17 So, my name is Doug Brash. I'm a
18 molecular biologist who hasn't thought about genetic
19 toxicology since I probably was a graduate student. I
20 think my role in here is to take what we know about
21 biology and see how much of it applies, and what can
22 we expect to see with regard to those four treatment

1 duration thresholds.

2 But there'll be a number of things I'm
3 going to say that are going to be obvious to some of
4 you. So, different things will be obvious to
5 different groups of you. But also, I think that
6 probably none of it's obvious to graduate students,
7 post-docs and assistant professors these day, who I
8 think largely don't think about these things.

9 And a big part of the reason for that
10 is that for the last 40 years there's been, in the
11 cancer world, almost an obsession with genes. And I
12 want to put that in perspective. So, let's see if I
13 can do this here.

14 So, the outline, I'm going to start
15 with why cancer is not just mutations, and then go on
16 to (indiscernible) affect those thresholds in the
17 literature. I'm not going to talk about tumors
18 because that's a (indiscernible). But for stress
19 signaling survival mutation, I'll show you kind of a
20 zoo of data and tell you what I think it's telling us.

21 And in my own world, I focus on skin
22 cancer, so I'll tell you a few things on melanoma, if

1 you don't know, I think that are relevant here. And
2 then in the course of reviewing all of this, I have
3 some opinions on things like linear agent and dose
4 responses and thresholds, and I'll tell you what, as a
5 biologist, the situation looks like to me.

6 So, ever since I was a grad student or
7 a post-doc, this is the way the cancer world has been
8 looking at cancer, near as I can see. And that's not
9 the whole story.

10 So, one way to think about it is, if
11 this were the whole story and what a carcinogen did
12 was solely to mutate genes, and you have 10 genes,
13 like five or six, that you had to mutate, well then,
14 the cancer incidence is going to be proportionally
15 (indiscernible) to the end. But that's not actually
16 what happens. It's a little more like it goes to
17 second or first power, and duration of exposure to the
18 fifth or sixth. So, there's some biology going on
19 here. And so, there are other things we'd have to
20 think about.

21 So, I think of this as the cancer cell
22 loop. And the genes are in the middle, but there's

1 things that go on before and things that go on after.
2 And people always at least think about the first few
3 steps. But I also want to talk about the last few.

4 So, we're going to start out with the
5 carcinogen and it's going to make a DNA lesion, and
6 it's going to make a mutation. That's going to happen
7 in some gene. That gene will have a phenotype of this
8 cell. And one cell never killed anybody, so you've
9 got to clonally expand that cell, and now eventually
10 you get to a precancer or a carcinoma.

11 But particularly for ultraviolet light
12 that I work on, in general, we know it's one of these
13 numbers. And as you (indiscernible) tendonitis
14 through her gene is cell generation. So, if you want
15 to hit five or six genes, or two of them, you also
16 find that six genes is even worse, this is not going
17 to happen in one cell. So, this end step here about
18 the clonal expansion, I think is the ballgame to
19 getting cancer to work at all.

20 So, yes, you would have to have a
21 mutation, but you also have to think about this clonal
22 expansion step. And in normal skin, we have clones --

1 I've got a picture of one -- that have one
2 (indiscernible). This happens to be p53, but not the
3 other ones. They're not even just sitting there as
4 single cells. They're growing as clones already, but
5 there's no obvious defect in the skin. I'll talk
6 about this more in a little bit.

7 And so, we go around and around this
8 cycle. And so you clonally expand. Now you've got a
9 bigger target, and now the carcinogen can
10 (indiscernible) or another carcinogen, you get the
11 second mutation and you keep going around. But now
12 you've even got the multiple (indiscernible) you need
13 to actually have a tumor. And people with sequencing
14 have now looked in normal skin at (indiscernible)
15 genes, and at the bottom is a cartoon of all the
16 (indiscernible) of the genes they did. And you see
17 there's even clones inside of clones. And this is
18 just 74 genes that they looked at.

19 So, by the time you get to be 60 or 70,
20 your skin is a saran wrap full of mutant clones just
21 waiting for something to go wrong. But it still
22 pretty much works as a skin anyway. So, that's what I

1 call the cancer cell loop. So, it's not just genes.

2 But on top of that, it's sitting in the
3 middle of a bunch of modulators. So, on the one hand,
4 you have metabolism, which could either get rid of
5 your carcinogen or activate it and make it worse. Or
6 you have repair, which is going to remove some of the
7 (indiscernible), maybe in time, before DNA
8 replication, maybe not.

9 Then there's this whole issue of
10 (indiscernible) transregional synthesis. I guess
11 we're (indiscernible). Anyway, so the point where
12 this comes along and it has a decision. Can it bypass
13 this legion? Is it going to make a mistake if it does
14 that? Is it going to block (indiscernible) the cell
15 dies? So, a few things can happen.

16 With regard to cell phenotypes, one of
17 them is apoptosis, so cells that are abnormal tend to
18 kill themselves. So, in a way, that's good, so that
19 they're not going to become cancer cells. But we'll
20 revisit that.

21 But (indiscernible) lesions can also
22 induce a re-differentiation of cells. People don't

1 tend to think about that prospect. I'll say something
2 in a minute. Just doing the (indiscernible) can have
3 a lot of gloss, so you're losing all (indiscernible)
4 for large regions of chromosomes. And that also can
5 be important, not only as a mutation mechanism, but as
6 already mentioned to initiation of promotion earlier.

7 And so, promotion, as most of you
8 probably know, would have an initiating event which is
9 probably mutagenic. Something later could happen, but
10 it doesn't matter unless you already have the
11 initiating event. And one of the things
12 (indiscernible) can be to the (indiscernible) is the
13 tumor promoter would be (indiscernible) if there
14 wasn't something wrong with the other (indiscernible)
15 it might be okay. So, there are multiple reasons why
16 it's important.

17 Now, these (indiscernible) so, now this
18 is all physiology that's superimposed by your
19 genetics. And many of these things are inducible.
20 So, you've got dose responses for inducing these
21 responses. And so, this is all pretty much
22 homeostasis at work. And it's largely helpful.

1 I mentioned differentiation. This is a
2 paper -- I thought it was really interesting -- from a
3 long time ago. I couldn't get anybody interested in
4 it, including Leo Sachs, who did it. But he was
5 inducing a differentiation with different chemicals.

6 And so, here is the list in his nature
7 paper, and what I really like is he even has the
8 carcinogenic and non-carcinogenic analogs in
9 polycyclic aromatic hydrocarbons, and the ones
10 inducing differentiation and the other ones don't. I
11 thought it was a great experiments, like he knew what
12 he was doing. But that's not what he was trying to
13 do. But anyway, it was a differentiation effect.

14 Then there's selection pressures. So,
15 you can have mutation (indiscernible), just like in
16 evolution, species evolution. We have mutations and
17 we have selection pressures. So in the case of UV and
18 p-53 in skin, what happens is the (indiscernible) of
19 apoptosis. It's great on the first trip to the beach.
20 You kill off the damaged cells before they can go on
21 to make a mutation. What happens on your second trip
22 to the beach?

1 Well, you've got (indiscernible)
2 mutations last time. You're going to kill off the
3 normal guys. The guy who's going to take their place
4 in the clonase band is the mutant, who is no longer
5 UV-sensitive. So, sunlight becomes a selection
6 pressure favoring the outgrowth of the mutants. And
7 in fact -- well, I'll show you how that plays out in a
8 minute.

9 Another way that this happens is the UV
10 in the presence of p53 changes the way cells behave as
11 stem cells or not. I won't go through it, but you
12 know, a stem cell can be two stem cells, or a stem
13 cell differentiated with two differentiated. You tip
14 that balance a little bit, and now you're expanding
15 exponentially if you make more of the stem
16 (indiscernible) divisions. And so that also is going
17 to (indiscernible).

18 Here is an experiment we did. I won't
19 tell you the (indiscernible) because it takes too
20 long. But in scan cancer, there's some stages that
21 depend on more mutations, and others that depend on
22 clonal expansion. So, if we found (indiscernible) to

1 bias the apoptosis rate, it affects the -- there are
2 too many double negatives, so I'll just tell you
3 without taking you through it.

4 If you have more apoptosis, that's
5 great we get rid of -- we have less of the mutant
6 requirement steps. But you get bigger clones during
7 the clonal expansion steps, which is just what we
8 would have predicted. But everybody always talks
9 about apoptosis as if it's this great anti-cancer
10 thing. Well, maybe. It depends on when. So, it's
11 not all that simple.

12 Now, the clonal expansion
13 (indiscernible) is the exponential growth is
14 important, because if you think about it, if you're
15 making mutations, each time you make mutations you
16 make some more, and the number of mutants is going up
17 literally. But if you're doing this clonal expansion
18 thing, you go out and mutant daughters (indiscernible)
19 exponential (indiscernible) really important.

20 Now, this clonal expansion may not be
21 so important for the present question of what happens
22 if you only get so many (indiscernible) wants. But

1 these other things like tilting differentiation phase
2 well may matter, if you can do that in one exposure,
3 for example.

4 Now, everything I showed you is still
5 sitting on the side of other stuff, more physiology.
6 So tumor promoters, or the self-proliferation state.
7 You know, if you've got a virus in your liver, it
8 matters whether you get a carcinogen superimposed on
9 that. And then there are microenvironment issues.
10 Inflammation is another one. So, it matters whether
11 your carcinogen is coming in through an inflammatory
12 environment. (indiscernible) down.

13 Then at the end of all this, you have,
14 hopefully, some immune surveillance that's trying to
15 get rid of these (indiscernible). And at the very
16 beginning, it's coming around to -- I think
17 (indiscernible) is ahead of everybody. There's some
18 messages the world does not want to hear. And I think
19 this is one of them, that cancers are polyclonal, and
20 there's not simply a single cell that's putting out.
21 There's more than just the one cell that matter. And
22 so, all these things factor in.

1 And so then we step back as a biologist
2 and say, do I even expect any kind of linear dose
3 response out of this? You would think that the actual
4 dose response has to look like this and it's going to
5 different from one person to another. And
6 (indiscernible) affect all this (indiscernible) stuff.

7 So, sorry I had to simplify things.
8 So, then, the lessons, I would say, for this part of
9 the talk, are the biology (indiscernible) no real
10 reason to expect a simple dose response is linear or
11 even monotonic. And then, if you think about why this
12 is, it goes back to (indiscernible) homeostasis
13 (indiscernible).

14 So, the cell is in many, many ways
15 trying to maintain a particular state. And on low
16 doses, the cell is doing that. And then at some
17 point, you're out of its operating range, and now what
18 you're doing, you're breaking the cell. And so,
19 whatever goes on when you're breaking cells is
20 different from whatever is going on when you're doing
21 homeostasis.

22 So, it seems to be (indiscernible).

1 There is no reason to expect you're going to be able
2 to take data from high doses where you're breaking
3 cells and extrapolate down what's going on in
4 homeostasis. There's just too many (indiscernible).

5 And then, how can homeostasis play out?
6 Well, it'd be partial, in which case you have not
7 quite as much effect of the carcinogen (indiscernible)
8 levels. Or it could be complete, and that could look
9 like a threshold. Or it could even overshoot and look
10 beneficial. And (indiscernible) I know in a couple
11 papers, that once you induce things (indiscernible),
12 you clear out other damage that's been accumulating
13 for other reasons just over the past 10 years or six
14 months in an experiment. And so that's really great.

15 And then what exactly happens, you
16 don't know in your case with your carcinogen and your
17 model, and probably your human volunteer, which is
18 probably more (indiscernible) until you do the
19 experiment. So, then you have this policy issue of,
20 well, if you don't know, what do you decide? And
21 (indiscernible) people (indiscernible).

22 Oh, and homeostasis depends on age.

1 So, the number one characteristic of aging is not that
2 your basal (indiscernible) go down a lot. It's just
3 that you can't depart very much without dying. So,
4 this is just one example of how much blood loss does
5 it take to kill a rat? Well, it decreases with age,
6 because they can't do homeostasis. But there are
7 similar experiments with (indiscernible) and so forth.
8 So, that also is going to factor into the
9 (indiscernible).

10 Now, so then the question is, well, if
11 I don't think should be a threshold, are there
12 (indiscernible) thresholds? Well, so let's go through
13 the data. And I'm not going to talk about cancer.
14 I'm just going to show you some data for signaling
15 survival in mutations.

16 So, on the left is an apoptosis. This
17 (indiscernible) experiment we did in apoptosis. But I
18 just want to point out (indiscernible). On the far
19 left one -- so, there's a (indiscernible) which is a
20 reparative (indiscernible) knockout mouse. Increasing
21 UV doses, how much apoptosis do I get? Well, so there
22 is a (indiscernible) increase. Looks like for the

1 wild type, there's a little curve at the bottom.

2 So, there is a little curve down here.

3 So, you could say, okay, great, there might be a
4 threshold. And then if you look here, there is not
5 (indiscernible). Here's p53 induction. Now you've
6 got different (indiscernible). MDM2 induction is
7 really interesting. You see it goes up and comes
8 down. Over here we have (indiscernible) this is a
9 repaired (indiscernible). And so it goes up and comes
10 down; so not linear.

11 And the (indiscernible) biology we
12 think about these things is we're not looking at how
13 things change from the y-axis. You need to look at
14 how things have changed on the x-axis, (indiscernible)
15 modification factor. What repair has essentially done
16 is scrunch everything to the left and it thinks it's
17 at a higher dose than it is, because it wasn't
18 comparing anything.

19 Now, why should it be that complicated?

20 Well, here's the biological circuit, so you

21 (indiscernible) it's supposed to be in charge of

22 apoptosis in this case. This is regulated by

1 (indiscernible) two, which is regulated by some other
2 guys, who form a loop with p53, and the notion is that
3 this all keeps p53 from turning on too much.

4 For UV, actually, the apoptosis done by
5 E2F1, and this is the modulator up here. And then
6 (indiscernible) loops here you've dose responses and
7 we don't know what they are until we actually do the
8 experiment. Again, that's, I think, a general problem
9 with what we mean by causality in biology. What do we
10 want to know here? You know, who (indiscernible).
11 So, that's why (indiscernible).

12 Survival dosage process. See, it's the
13 same sort of theme. This is the classic. So, if the
14 repair defect of this -- repair defect goes in a
15 straight line, increasing those, goes straight down
16 (indiscernible) kill it. If you can do repair,
17 there's (indiscernible) here which kind of looks like
18 a threshold, and now eventually you get to something
19 like when we do loglinear (indiscernible).

20 Loglinear, what that means is that each
21 (indiscernible) increase kills the same percent it
22 killed in the (indiscernible). So, you kill a certain

1 percentage in the first (indiscernible) dose.
2 Whatever is left, you kill the same percentage
3 (indiscernible) that's going to get a straight line no
4 matter what occurs. And it's almost like the
5 (indiscernible) hypothesis (indiscernible) kill
6 something (indiscernible) there.

7 And these other guys would just show
8 you that, well, this is the (indiscernible) of the
9 thing, and it doesn't really matter. You see it with
10 other kinds of agents and other kinds of
11 (indiscernible). So, over here is your
12 (indiscernible). The shoulder is your homeostasis
13 part, and here is (indiscernible) cell part.

14 Now, mutations. So, this is HPRP for
15 alpha rays which are considered non-repairable
16 (indiscernible) on a straight line. You see the other
17 guys are mostly kind of curvy and (indiscernible)
18 different (indiscernible), while being resistance is a
19 similar sort of thing.

20 It doesn't depend on drug selections,
21 so here is something (indiscernible) whether you're
22 just (indiscernible). You can see these guys are --

1 the ones at the bottom are wild type and these are
2 (indiscernible) where it goes. So, great.

3 (indiscernible) graph (indiscernible)
4 are almost always not (indiscernible) on
5 (indiscernible).

6 MAN: We can't hear you over here.

7 DR. DOUGLAS BRASH: Oh, okay. So, the
8 mutation plots are not usually plotted to the model.
9 Oh, yeah, before I go there, I want to show you one
10 other cell. Here's an example where you see -- so
11 this is a mutation (indiscernible) still plotted in
12 the ordinary way.

13 You see this increase here has a little
14 bit of a curve down here. What they did in this
15 experiment (indiscernible) they (indiscernible) cells
16 and let them get different lengths of time before DNA
17 replication. How close can you get to DNA
18 replication? And if you get really close in DNA
19 replication, you start seeing this little curve.
20 These guys are linear, but that just means you had
21 enough time to do repair.

22 So, this little curve down here, you

1 notice it's sloped; it's the same as this other one.

2 MAN: (indiscernible) closer to this
3 microphone.

4 DR. DOUGLAS BRASH: So, it's not really
5 so much that there was a threshold dose. It's just
6 that you didn't have this catastrophic effect of UV
7 radiating the cell right next to DNA replication.

8 Now, the other thing I want to talk
9 about. So, (indiscernible) plot mutations on a log
10 scale, right? So, there are some papers that do that.
11 And now, what does it look like now? Well, you get --
12 you're not really seeing anything that looks like a
13 threshold. In fact, it's quite steep near zero. So,
14 why was this (indiscernible) highest (indiscernible).
15 It's in the first finger of the (indiscernible). Oh,
16 well, okay. (indiscernible) more survivors. But this
17 is mutations per survivor. So, that's not it. So,
18 what's going on here?

19 Here's a paper from (indiscernible)
20 where they actually brought in the exact same data,
21 but (indiscernible) if you look at it on a non-log
22 plot, you'd say, oh great, a threshold (indiscernible)

1 down (indiscernible) it goes. And if you plot it on a
2 log plot, you'd say, oh wow, most of the action is
3 down here at (indiscernible). So, what's going on?
4 Why is this?

5 And it dawned on me as I was thinking
6 about this that, oh, this is actually just algebra,
7 although it's going to be misleading algebra. What
8 happens is that mutation frequency, mutations per
9 survivor, so that's mutations per initial cell divided
10 by surviving cells per initial cell.

11 Surviving cells per initial cell is not
12 just survival. Mutant cells per initial cell is
13 something nobody ever talks about. You know, it's not
14 a thing. But if you do that, you see what you're
15 going to have is one line is an exponential divided by
16 an exponential, and no wonder you get these funny
17 curves. And so, if you plot that on the log, you get
18 the shape that I was telling you about. But if you
19 plot this same thing (indiscernible) ordinary way,
20 non-log, well, it looks like we have a threshold.

21 So, I'm now really suspicious of
22 thresholds, and I think it'd be important to be really

1 clear on what our definition is on that threshold.

2 And I'll come back to that briefly again.

3 So, conclusions, two. Survival seems
4 to show a real threshold, as reflected in homeostasis,
5 unless the cells are repaired efficient, which is
6 going to matter when you're looking for volunteers
7 (indiscernible) homeostasis (indiscernible).

8 Mutations can show a pseudo-threshold, if you're not
9 plotting it as a log, in one of these two ways. That
10 absence of the catastrophe curve or this
11 (indiscernible) consequence.

12 So, lessons from (indiscernible) about
13 thresholds and single exposures. These are more or
14 less just (indiscernible), but they're indicative of
15 things that we saw a lot of in the last talk. So,
16 there's evidence of melanoma cells, or cells derived
17 in tissue culture that came from a melanoma tumor are
18 in fact deficient in post-replication repair.

19 Then there is something that -- we've
20 got a paper coming out on in a few weeks that I call
21 attention to this -- but there are recurrent
22 (indiscernible) mutations in (indiscernible). The

1 mutation (indiscernible) are 100 percent
2 (indiscernible), which is the UV signature. And it
3 shouldn't be 100 percent. It should be 60, 70, 75
4 percent, maybe, and a repair effect of like
5 (indiscernible) pigmentosum patient, this may be 90
6 percent. So why are they 100 percent? So does that
7 also tell us that the patient or the cell became a
8 melanoma was (indiscernible).

9 So, Dr. (indiscernible) your volunteers
10 have a (indiscernible) dose. And so that would be
11 just for survival.

12 Then there's single UV exposure story
13 in melanoma. There's a couple of them. So, the
14 famous one, (indiscernible), is that
15 epidemiologically, there's a correlation predicting
16 risk. Sunburns in childhood are a strong risk factor.
17 And so the notion is that after you get a strong
18 sunburn in childhood, you did something and that
19 predisposes you to a melanoma (indiscernible) years
20 later.

21 There are some caveats. Sunburns in
22 middle age could also increase your risk. And sunburn

1 could just be a (indiscernible) of skin type
2 (indiscernible) like fair skins. Oh, I should say
3 that you may or may not know that product sunlight
4 exposure, which is to say farmers and fishermen get
5 basal squamous carcinoma through (indiscernible)
6 cancer, and that seems to be a little bit protective
7 with melanoma.

8 And then there is this whole other
9 story about melanoma being correlated with childhood
10 sunburns. So there is this notion in the melanoma
11 field of acute exposures. How solid or flimsy that
12 is, I don't know.

13 But motivating that, people looked in
14 mice and they gave mice a (indiscernible) on UV
15 exposure, then you can get melanomas. And those
16 melanomas have UV signature mutations. There's a
17 caveat. These are transgenic mice. First of all,
18 mice don't have melanocytes in the epidermis, so you
19 break from (indiscernible). And then there are other
20 genes to knock out. And then the notion is that,
21 well, okay, (indiscernible) some of the steps, but we
22 can at least do an experiment in a reasonable time.

1 You could ask whether, okay, waiting for those other
2 steps is what took a long time and why this is not
3 working (indiscernible).

4 Then there is a paper that just came
5 out from the (indiscernible) lab. They did four UPV
6 plus UVA exposures and they got melanomas sooner than
7 when they did clonic exposure. Which, again,
8 reiterated some of what you heard in the last talk.

9 So, what are the mechanisms for the
10 single exposure effect? So short answer is we don't
11 know, but there are a few things proposed. The
12 classic one, and the quite reasonable one, is that
13 single UV exposure does make melanocyte proliferate.
14 So the notion would be, okay, now you're stimulating
15 the cells from (indiscernible). And then that's now
16 written into your genome.

17 There's a more central story, which if
18 anybody gets interested, I wrote a "News and Views" on
19 it, so you can find it on (indiscernible) on somebody
20 else's experiments. But there's a feedback
21 (indiscernible). One is you can induce melanomas in
22 tissue cultures with just growth factors and no

1 mutagens at all. And you get the melanoma anyway.

2 It's reversible.

3 Then what the Walker lab did,
4 (indiscernible) is they used a (indiscernible) cross
5 to ask, okay, if we make all these mice with different
6 genotypes, can we find polymorphisms that will
7 accelerate the neonatal UV phenotype, neonatal
8 (indiscernible) phenotype.

9 So, they went to all this work, and
10 what they found was that there were just a couple of
11 genes that do this. And what they do is there are
12 (indiscernible) related genes that are UV inducible.
13 So it looks again like they're doing something with
14 physiology. UV is changing the physiology of a cell
15 and that somehow accelerated (indiscernible).

16 And in this paper, we've shown that
17 your gene (indiscernible) single basis for UV
18 (indiscernible) which we cite (indiscernible) that are
19 a hundredfold more likely to get a (indiscernible)
20 from elsewhere. These are sitting in regular
21 (indiscernible) genes. They're sitting in some of
22 these recurrent mutation sites. And they're so

1 frequent, the mutation frequency is now on the order
2 of one percent. And so, every -- oh, and
3 (indiscernible) certain metabolic pathway.

4 So, if you go to the beach, every one
5 of your cells is going to get hit in every one of
6 these pathways at least once, given (indiscernible).
7 So, it's almost like an epigenome mark now. And
8 whether this is required for cancer to be able to
9 (indiscernible).

10 Another (indiscernible) from a paper
11 from Jimmy Cleaver, which I think got kind of buried
12 in the (indiscernible), but I think it's really
13 important. What they have, they were trying to do
14 deep sequencing of UV-induced mutations. And they
15 started out with (indiscernible) cells, but you don't
16 want to have to keep using different cells strains.
17 Well, that turned out to be a bad idea because
18 (indiscernible) cells have 10 to hundredfold higher
19 background mutations (indiscernible) it's just a
20 spontaneous mutation.

21 Then they went and (indiscernible)
22 radiated them and the mutation frequency went down,

1 not up. So, that's just kind of (indiscernible). So
2 what is happening here? And so the bottom panel
3 (indiscernible) look more closely at what these were.
4 And so, what they have in the spontaneous
5 (indiscernible) cells were (indiscernible), subclones
6 -- you get these big clones, little clones -- and what
7 happened was that the UV exposure was killing off the
8 little UV clones and sort of favoring the large
9 (indiscernible) clones. And so, they were thinking
10 about this (indiscernible) on one hand is it
11 (indiscernible), or on the other hand, just a little
12 bit like things that happen in a species' evolution,
13 where you constrict the number of genetically
14 different individuals in the population.

15 So, again, there is something that can
16 happen. It's sort of like purifying selection in
17 evolution. And it could happen with a single UV
18 exposure. So, the conclusion here is that melanoma
19 may involve some no-threshold and single-threshold
20 (indiscernible).

21 And then last, I'm going to go out of
22 my area of expertise and just make some comments on

1 some things that I noticed as I was going through some
2 of this literature for this meeting. Although it's
3 sort of relevant to things that we have to deal with,
4 like the question is, oh, is it bad to get a sunburn,
5 is it bad to get a tan? And how does that affect your
6 risk?

7 So, the number one thing that amazed me
8 -- I have to say, I started reading some of the
9 (indiscernible) in particular, with the hope of
10 identifying what the errors were. And I came away
11 more impressed than with a list of errors. However, I
12 did find a few things. So, this is a graph from a
13 paper that was (indiscernible) is officially a part of
14 the (indiscernible) journal issue around -- with
15 different people commenting on it.

16 So, they're talking about -- so this is
17 an example of a non-linear threshold. Okay. Well,
18 what was the equation? Well, it's $r=ADQ$. And $r=ADQ$,
19 if I follow it on the log, it's going to be a straight
20 line. If I magnify this part of it, it's going to
21 just look like that. So, it's a terrible example of
22 the threshold. It's just not really there.

1 And so, if this the kind of thing
2 people are dealing with in threshold, then you've
3 really got to get a handle on (indiscernible) of the
4 question.

5 Now, they have a linear model that had
6 its own sketchy origins, going back -- this is mostly
7 taken from Calabrese's paper. First, I understand it
8 was (indiscernible) present. We're going to have to
9 trust him on the history digging that we do. A bit of
10 a character, but I think we (indiscernible).

11 So anyway, initially, a lot of this
12 started with just target theory. Talking about a
13 physicist. This would be before we knew about repair
14 and any of these other homeostasis things. And so the
15 idea was we would just have like numbers
16 (indiscernible) exponential (indiscernible). So there
17 at the time, except they never published the
18 calculations, so it's a little bit scandalous, I
19 think. (indiscernible) calculations (indiscernible)
20 hit on that.

21 Then the next generation, you had the
22 (indiscernible) mouse experiments, which were an

1 attempt to actually major frequency (indiscernible).
2 But I guess there was -- or I'm gathering there were
3 statistical errors in the control population.

4 Then there came the models. Too bad
5 Kenny couldn't be here, because he could explain all
6 this better than I. But you have these various
7 mathematical models and then you ask how they can
8 extrapolate down to a (indiscernible)?

9 Well, one of them was the idea that the
10 mechanism must be the same for spontaneous and
11 genotoxin-induced cancer. But we know that can't be
12 right, because we see different (indiscernible)
13 mutations in spontaneous cancers and reduced ones.
14 So, they are different things.

15 But all of these models -- and this is
16 important (indiscernible) -- for everybody to keep in
17 mind that I have to deal with daily whenever I'm
18 dealing with (indiscernible). Whenever you've got an
19 equation or a model, there is some assumption
20 underway. You've got to find out what those are,
21 because you don't what the guys assuming. And
22 particularly if he's pulling off programs off the

1 shelf. And are these models assuming (indiscernible),
2 just to be (indiscernible) or something, for example.
3 Are they assuming this, that or the other
4 (indiscernible)?

5 So, I've listed here some of the
6 assumptions that go into these models. I'm in no way
7 competent to judge any of these models. But these are
8 the things we should all be asking your bio
9 (indiscernible) and model makers, hey, what about
10 this?

11 So a lot of the assumptions in those
12 early models -- and I haven't even looked at the main
13 ones; I got up to about like 1980-something -- thought
14 that there would be a chronic exposure, assumed the
15 tumors were (indiscernible) clonal. But there's no
16 growth advantage until all the hits occur, so that,
17 you know, each driver is not contributing, in those
18 early models, anyway. Nothing happens between here to
19 the end.

20 And now there's a concept of backseat
21 drivers, which are the strong (indiscernible) drivers,
22 but I think that's a little closer to the

1 (indiscernible) truth.

2 Then also the assumptions that cancer
3 increases monotonically (indiscernible). Not an
4 experimental observation. An assumption that went
5 into the equation. Okay? And things like no repair
6 or cell death.

7 And I was looking at a recent review of
8 Kenny (indiscernible), and he was kind of -- seemed to
9 me, despairing of actually having a biology-based
10 model, because it's too complicated. And I have to
11 sort of sympathize with that. And I have some
12 thoughts. We'll save it for discussion, as to what
13 may be an alternative to coming up with theoretical
14 dose responses. But I can save that for later.

15 So, here then are (indiscernible) which
16 I guess the terminology has moved to (indiscernible)
17 responses is just a way better idea, because
18 (indiscernible) is so (indiscernible). And I see
19 didn't people see different percentages in this. But
20 it seems to me it happens. It seems to be what you'd
21 expect homeostasis. There have been a few things
22 (indiscernible) there, because you haven't broken the

1 cell. The cell is trying whatever this is you're
2 doing to it.

3 And so, it seems to me a reasonable
4 phenomenon. You don't know whether it's happening to
5 you in your system and your carcinogen or not until
6 you do the experiment. But I think there are some
7 conclusions, nevertheless, that you can draw. So,
8 here are my overall conclusions.

9 One is that biology offers no reason to
10 expect a linear or monotonic dose response or expect a
11 fresh (indiscernible). You might find one
12 (indiscernible). Homeostasis implies that the
13 (indiscernible) within the system's operating range, a
14 genotoxin will have a smaller impact, for some reason
15 or another, at that low dose, because your cell is
16 trying.

17 Yet -- and this is not my analogy; it's
18 something else having to do with the skin cancer --
19 even if that's true, it's not a good idea, just
20 because your office has a fire department, doesn't
21 mean you set fire to your wastebasket to turn on the
22 fire sprinkler to prevent a fire. And so, say we did

1 have low levels of radiation everywhere. And say we
2 even have a homeostatic (indiscernible) protecting us.
3 That's not a good reason to say to say we should have
4 our fire sprinklers on all the time, I don't think.
5 That's a little different from today's question where
6 you're talking about just one or two doses. But
7 still, I don't think we would want to (indiscernible)
8 on (indiscernible) as an operational living principal.

9 Then if you see toxicity, that means
10 you're outside the operating range, so you're breaking
11 the cell. And that (indiscernible) is different from
12 breaking homeostasis (indiscernible) extrapolate one
13 from the other.

14 For survival, there do seem to be
15 thresholds if the killing is due to reparable lesion
16 and the cell is repaired proficiently.

17 (indiscernible) So that gives you some hope, but the
18 question is, okay, do we know which does range we're
19 in (indiscernible) percentages.

20 And for mutation, there is a no obvious
21 threshold dose that I can see. Because the low dose
22 has had a larger mutation frequency per dose. Now,

1 you could ask yourself, do I care about the mutation
2 increase per dose, the steepness of the curve, or do I
3 care about the absolute value?

4 And that's a little bit like asking do
5 I care how much the interest rate is on my money, or
6 do I only care about the amount of money I have? And
7 I could be getting six percent as a post-doc and not
8 have very much money in my bank account, I still get
9 six percent when I'm about to retire, but it's a
10 little more money by then. But it's been six percent
11 the whole time.

12 So then the question is which do you
13 care about, the total mutation prevalence or the rate
14 at which you may (indiscernible). And then, that
15 pretty much covers that.

16 And then we have these dilemmas, which
17 I will only spend one minute on because it becomes
18 apparent. So, do we have thresholds? Do we
19 (indiscernible) on a threshold if we can't measure it?
20 Single exposures, do we (indiscernible) that they're
21 harmless if we haven't done the experiment?

22 And then this ethical question of like

1 how close to the railroad tracks do we want to let our
2 kids play? You know, if it's a gray area where we
3 can't measure it, what kind of decision do we make?
4 And then the question of who decides on
5 (indiscernible) add other (indiscernible). This might
6 stuff might be on the end, but okay.

7 And if I can answer questions...

8 DR. AISAR ATRAKCHI: Are there any
9 questions?

10 MAN: Well, thanks a lot for that talk.
11 That was great.

12 DR. DOUGLAS BRASH: Uh huh.

13 MAN: I haven't seen some of that data
14 for (indiscernible). Thank you, thank you.

15 MAN: (indiscernible)

16 DR. DOUGLAS BRASH: The person who
17 should really be here is (indiscernible).

18 MAN: So, you really sit a spell with
19 someone who (indiscernible). Unfortunately, most of
20 the people associated with it are either dead or
21 retired.

22 MAN: (indiscernible)

1 MAN: I was wondering if you have a
2 (indiscernible) the EMS that was generated with the
3 (indiscernible) if you have an (indiscernible) issue
4 where they claim to have a threshold or a practical
5 threshold permutation that was used to develop a
6 (indiscernible) decision that there was no risk
7 associated with the EMS examination that was
8 experienced by some patients.

9 DR. DOUGLAS BRASH: I haven't seen it.
10 I'd be interested --

11 MAN: (indiscernible)

12 DR. DOUGLAS BRASH: Yeah. Did they
13 have (indiscernible) basis for why there was such a
14 (indiscernible)?

15 MAN: DNA repair (indiscernible) was
16 reducing the (indiscernible). But it was a situation
17 where there was a really high -- this is a transgenic
18 rodent (indiscernible) where they showed a shoulder
19 and then an increase in (indiscernible). But there
20 was a really big background to this assay, with a big
21 range, depending on how many animals you used in it,
22 as far as the standard deviation.

1 So, you mentioned the mega mouse
2 experiment. It looks for the world that the bladder
3 tumor incidents looks like a threshold with response,
4 but would you really look at the statistical data if
5 you have any kind of background at all with an error
6 associated with it? It's almost impossible to
7 distinguish at a low level of exposure whether or not
8 you're dealing with a true threshold or just a shadow
9 of dose response, because you're always within the
10 (indiscernible) at low doses.

11 I was wondering how you feel about
12 using benchmark dose rather than (indiscernible) for
13 accepting (indiscernible) acceptable limits.

14 DR. DOUGLAS BRASH: So, you might not
15 be -- so, since I'm an amateur in this --

16 MAN: Okay. Maybe I'm getting into the
17 wrong (indiscernible). All right. I'll
18 (indiscernible). But I wouldn't hear about it, but
19 okay.

20 MAN: Maybe (indiscernible).

21 DR. DOUGLAS BRASH: I guess the answer
22 is I don't have a current feeling, but I may have to

1 fill you in.

2 WOMAN: So in the mega mouse study,
3 (indiscernible) on a parallel study (indiscernible).
4 And in the bladder, the adducts were (indiscernible)
5 but the idea was that the threshold was caused by an
6 event (indiscernible) this (indiscernible) profile.
7 So, at a certain dose, you increase (indiscernible),
8 and that's when the tumors (indiscernible)? But you
9 had adducts (indiscernible) adducts plus
10 (indiscernible)?

11 DR. DOUGLAS BRASH: So, that would be a
12 nice mechanistic reason.

13 WOMAN: Yeah.

14 DR. DOUGLAS BRASH: Yeah. And then the
15 question is how do you ever know in each particular
16 case if that was going on.

17 WOMAN: Well, you don't.

18 DR. DOUGLAS BRASH: Yeah.

19 WOMAN: Obviously.

20 MAN: I'll admit it's (indiscernible).
21 Well, in addition to the mega mice study, of course,
22 there's the mega rat study (indiscernible), and

1 there's the (indiscernible) study on (indiscernible),
2 which were intended for higher numbers. And we
3 vandalized all that data as well for the
4 (indiscernible) agency in the U.K., in trying to
5 justify the numbers they've used to permit a genotoxic
6 substance in food.

7 And as you'd expect, the answer is you
8 cannot say with confidence in any of those studies
9 that there is a threshold, based on the empirical
10 observation, because you're not at the range of the
11 acceptable risk in humans. And so you need diagnostic
12 studies, and they don't exist for the majority of
13 those data.

14 DR. DOUGLAS BRASH: It's almost like
15 we're in position with the military. You have to make
16 that decision, but you don't have enough information,
17 and it's serious, but what do you do?

18 WOMAN: Thank you for the presentation.
19 I really enjoyed it. Seems from the one conclusion
20 that no (indiscernible) cannot be (indiscernible) from
21 the high (indiscernible). And this also
22 (indiscernible). So, in the clinical situation, the

1 (indiscernible) is very (indiscernible) almost on the
2 (indiscernible) him speaking. Therefore, it's very
3 hard to make call whether we can do the
4 (indiscernible) test (indiscernible) for that when you
5 find at very high dose the animal model and you see
6 the (indiscernible). So I did not see from today's
7 discussion (indiscernible).

8 So, my question is how to
9 (indiscernible) a rat, whether we are allowed
10 (indiscernible) we know the (indiscernible) low, much
11 lower compared to the observed (indiscernible) animal
12 model.

13 MAN: Yeah. I agree --

14 DR. DOUGLAS BRASH: I'll just say then
15 one word about what I was going to say and decided to
16 postpone until the discussion. Getting a dose
17 response is more than any kind of equation, you're
18 taking -- what made me really think about this was you
19 raised, I think, the issue of weight -- somebody had
20 mentioned the issue of weight or reference is that
21 relating to. And what does that even mean?

22 And if you get any kind of equation,

1 you've got -- okay, so it's Ames-positive,
2 micronucleus-minus. Do those cancel each other? Do
3 they add? Or you know, what do they do? And so
4 there's two general kinds of computations. One's
5 called a blending computation, where you just kind of
6 mix things up and out comes the numbers.

7 The other sort of thing, there's a
8 thing called a particular principle, and this is the
9 way genes (indiscernible) is you've a gene for red, a
10 gene for white. You mix them, you don't get a pink
11 gene, you get a pink cloud. Okay? And you retain at
12 the beginning the identity of the individual compounds
13 at the lower level. But it requires this hierarchal
14 computation. So, what I'm wondering is whether the
15 solution to this -- well, it would be nice to get
16 better vision so you could make (indiscernible).

17 But the other stuff, we've essentially
18 got a whole bunch of carcinogens that we know a lot
19 about. Can you come up with basically a clustering
20 scheme where you find out, okay, there's 30 different
21 groups of known carcinogens. I've got a new chemical.
22 Which of the 30 does it (indiscernible) based on all

1 of the tumors that we know about? And then there
2 would be a way of getting the information that we
3 don't really have. And then this only works, of
4 course, if you're on clusters.

5 WOMAN: Thank you.

6 DR. AISAR ATRAKCHI: As I mentioned
7 earlier, Dr. Crump wasn't able to be with us today due
8 to a death in the family. We're going to try to get
9 some of the high points of his presentation. We had
10 originally reached out to Dr. Crump as a mathematician
11 and might be able to provide some estimate of the
12 cancer risk, the low number of doses of a Ames-
13 positive drug. It was sort of our original motivation
14 for reaching out to him.

15 And I'm restating the question for the
16 workshop here. And an acceptable answer to this
17 question was somehow take into account some measure of
18 the (indiscernible) genic or injected carcinogenic
19 potency of the drug. Even though we have a full suite
20 of typical data on the drug candidate, making credible
21 estimates of cancer risk would be very difficult.
22 Most of these data would be typically from chronic

1 exposures (indiscernible) short-term level exposures
2 would require (indiscernible) data on chronic
3 exposures, making (indiscernible) of this
4 (indiscernible) impossible to extrapolate from
5 chronic exposures to the (indiscernible) doses.

6 He's premising to some control of human
7 inhalation exposure studies. I'm going to leave this
8 to you to look at. I will try to forward this audio
9 presentation in the next few days.

10 On (indiscernible), rather than
11 estimating a risk, he sort of came up with a model
12 that we might be able to use, using a (indiscernible)
13 chemical. For this exercise he chose a nitrite as the
14 comparative chemical. And that nitrate seems to be
15 unique and then it's an Ames-positive chemical that
16 (indiscernible) present in (indiscernible) small
17 amounts. And it's positive in TA-100. And he's
18 stating here that nitrate has not been shown to be
19 carcinogenic. And yet he did two-year carcinogen
20 studies in mice and rats that seem to be negative.
21 However, IR has -- I don't know if it's listed --
22 nitrate is probably a carcinogen, based on use in food

1 as preservative. Maybe the panel could discuss this,
2 if they choose to go down and talk further about this.

3 He notes that (indiscernible) allows a
4 maximum consumption of some (indiscernible) containing
5 200 parts of (indiscernible) nitrite, and this would
6 be equivalent to 17 milligrams of nitrate per three-
7 ounce serving of fish. The WHO maximum daily dose is
8 .13 kilogram of nitrite. This would be equivalent 8.9
9 milligrams for a 150-pound person. And the WHO
10 maximum recommends daily intake of .05 milligrams or
11 kilograms of nitrite. It's equivalent to 3.4
12 milligrams.

13 More or less, he's wanting to use
14 nitrate to employ this as a comparator in the Ames
15 assay. I can't really speak to his math. More or
16 less, he wants to use nitrate as a comparator in the
17 Ames assay with a chemical of interest. He's making
18 reference to (indiscernible) with 1997 paper, where
19 protecting (indiscernible) on the Ames assay.

20 He suggests that nitrate may be tested
21 concurrently with a candidate drug using the same
22 experimental protocol, same salmonella strains,

1 (indiscernible) protocol, et cetera. He suggests that
2 the lower bound be used as a maximum (indiscernible)
3 exposure rather than a (indiscernible) estimate.

4 Decisions would need to be made
5 regarding how to use the data from those strains
6 (indiscernible) protocols, use them to find maximum
7 (indiscernible) exposure. This approach could not
8 place any restriction on the number of days a
9 volunteer could be exposed. This is in keeping with
10 the fact that based on the maximum daily exposure
11 limit, or nitrate, which also do not have such
12 restrictions. Prudence would dictate that exposures
13 should only last for the minimum number of days
14 (indiscernible) answer the scientific question.

15 Exposure to the drug candidates'
16 maximum daily exposure will entail some mutagenic
17 potential, as exposure to an amount of nitrite
18 allowable by U.S. FDA (indiscernible) positive
19 chemical (indiscernible) found to be capable of
20 causing cancer.

21 Here he is showing the positive for
22 sodium nitrate and ta-100. He's also comparing it to

1 some other known carcinogens. Here he is
2 (indiscernible) the potency of Allyl Urea versus
3 sodium nitrite. Here sodium nitrite is supposed to
4 have a higher potency. Here there is (indiscernible)
5 amino azobenzene, here (indiscernible) aminozobenzene
6 is a higher potency. The idea would be to use the
7 slope of the line to slope the dose response to sort
8 of a maximum daily exposure.

9 And aminoazotoluene, again, has a
10 higher (indiscernible) count than sodium nitrate,
11 which is the comparator. Similarly, for another
12 carcinogenic, it also has a higher potency than sodium
13 nitrate.

14 This is all in his essay.
15 (indiscernible) of this approach is straightforward
16 and easily implemented. Takes into account the
17 mutagenic potency of a drug candidate. Does not
18 restrict the number of days that the (indiscernible)
19 exposure per day. It's based on the precedent sent by
20 U.S. FDA. (indiscernible) positive chemical.

21 This approach ensures that maximum
22 daily exposure for a candidate, drug has an equal

1 (indiscernible) FDA's maximum daily exposure for
2 nitrite. And then he's basically using the slope of
3 the dose response (indiscernible) it's curved to
4 (indiscernible) maximum daily exposure.

5 And I guess the panel could address
6 this this afternoon. Thank you.

7 MAN: If you're compelled to respond,
8 because my name was flashed all over the place. But
9 one point that hasn't been made is this all assumes
10 that there is a correlation that goes -- a potency
11 correlation between Ames-test mutagenicity and rodent
12 carcinogenicity. And if there's going to -- this
13 afternoon, I have a slide that shows that the
14 correlation is zero. Approaching zero.

15 The thing is, the Ames-test potency
16 doesn't even correlate with other in vitro endpoint
17 tests of (indiscernible). The Ames-test potency and
18 (indiscernible) potency do not correlate. So why
19 would you expect it to correlate with carcinogen
20 (indiscernible). And it assumes he doesn't. And
21 essentially, everything that these graphs show assumes
22 a correlation.

1 WOMAN: Yes. And this is the math that
2 he suggested -- he couldn't really answer our direct
3 questions.

4 MAN: (indiscernible)

5 WOMAN: He also (indiscernible)
6 critical. What is the threshold (indiscernible)?

7 WOMAN: (indiscernible) the last
8 question because he's not here. But what slope is
9 critical? So at what point do we say this is not safe
10 and not given (indiscernible). And what slope is okay
11 to give? And if it's okay to give, how many doses do
12 you give? So, I mean, this might be a start, but
13 there are lots of steps I think that needs to be
14 filled.

15 WOMAN: (indiscernible) the assumption
16 that nitrite is a model for all chemicals. I mean,
17 that's really a problem. Carcinogens do a lot of
18 different things, so it's gene (indiscernible). And
19 chemicals, you just can't (indiscernible) them
20 (indiscernible) that they won't (indiscernible) and
21 that's (indiscernible), which otherwise is a reason
22 why (indiscernible).

1 MAN: I do want to call out the
2 concepts here, because I think there is merit to the
3 concept. And that is it's trying to -- it's talking
4 about quantity of risk against something that I think
5 we understand, in this case something that is sodium
6 nitrate, at which level we think is safe. So, it's
7 (indiscernible) to compare that, an unknown to a
8 known. And we could also compare where that unknown
9 to a known hazard as well. That's not something we
10 typically do.

11 I think even in a (indiscernible)
12 consent, going back to the bio (indiscernible) talk,
13 if there's an (indiscernible) that, you know, your
14 risk in this is in the ballpark of getting a dental x-
15 ray. It's an experience shared by everybody. That
16 would resonate. Maybe they would have better
17 communication that way.

18 I think the flaw in this particular
19 approach, of course, is that the metabolic
20 (indiscernible) is sodium nitrite is going to be
21 different, very likely different, from whatever
22 chemical it is that you're testing. (indiscernible)

1 contrast agent, which is 10 to the 10th years. Is
2 that a half life or is that a (indiscernible) life?

3 You know, I wonder what the slopes
4 would be between sodium nitrite and something like
5 that. I think that explains that the lack of
6 correlation in terms of potency. So, this is flawed,
7 but I do want to call out that concept because I think
8 there's merit in there.

9 MAN: Just try to show you
10 (indiscernible) doses he was proposing (indiscernible)
11 at the bottom row, the lower bound, like for
12 (indiscernible) he's saying, according to
13 (indiscernible), 58 were -- I guess the lower bound,
14 he was proposing to administer the lower bound. And
15 I'm not trying to endorse his proposal. I think that
16 was what he was trying to get at.

17 I think we're scheduled to have lunch
18 from 12:00 to 1:00. The panel discussion will begin
19 at 1:00 P.M.

20 (Break)

21 DR. AISAR ATRAKCHI: Okay. Good
22 afternoon, everyone, and welcome back to the second

1 session of this important workshop. I am Aisar
2 Atrakchi. I'm a pharmacology toxicology supervisor in
3 the Division of Psychiatry at CDER and I am a co-
4 organizer of this workshop.

5 In the morning session, you heard Dr.
6 Robison's introduction and background for why we are
7 holding this workshop with the emphasis on a few key
8 words: Healthy subjects, number of doses, mutagenic
9 DNA reactive drug, and cancer risk estimate.

10 We heard why this information is of
11 importance and the roll it's played in the development
12 of generic drugs, discussed by Dr. Dorsam, where
13 clinical bioequivalents, clinical study, enrolled
14 healthy subjects relying on the information of the
15 listed referenced drug as stated in the drug label,
16 and also the importance of this for the beginning --
17 the early stages of drug development Phase 1.

18 This paucity of the information on the
19 topic of this workshop was clearly presented by Dr.
20 Petibone through the results of the extensive and
21 exhaustive literature search that he and Dr. Shemansky
22 carried out over the last year for many months, and

1 continue to do so.

2 We also heard from our two experts in
3 the field, Dr. Brash explaining the process and steps
4 encountered from a mutation to tumor induction and the
5 role of pills, dose rate, and duration of exposure and
6 the presentation by Dr. Crump, at least the slides,
7 using mathematical and statistical approach to cancer
8 risk prediction.

9 We also heard from Dr. Prohaska
10 addressing the ethical issues and concerns enrolling
11 healthy subjects in clinical trials. For this
12 afternoon's session, we have assembled some of the
13 best experts in the relevant scientific fields and
14 have prepared a number of questions to engage and
15 stimulate the discussion, including the points made in
16 the morning session.

17 At the end of today, we hope to gather
18 information from the panel discussion that will advise
19 and assist the agency to better understand the current
20 scientific thinking of allowing safe dosing of a
21 mutagenic DNA reactive drug to healthy subjects
22 without increasing their cancer risk.

1 So with that, I'm going to go through
2 the first question, but some of those questions are
3 also repetitive, more or less, but -- and I tried to
4 gather, to put some of them together to address at the
5 same time. So question one, how many doses of an
6 Ames-positive drug, DNA reactive drug that can be
7 safely administered to healthy subjects?

8 Can it be administered at all? One
9 dose, two, or up to four doses? And if it is okay to
10 administer these one or more doses to healthy subjects
11 are acceptable with a mutagenic, how should the study
12 be designed? I think let's go to first through the
13 first question and then we'll go -- move on to the
14 next one. If it's okay, then we'll move to the next
15 question.

16 So what I would like to do is, if
17 possible, starting from my left, introduce the panel,
18 introduce yourself with -- and your affiliation and
19 very brief background.

20 DR. ROBERT HEFLICH: Hi. My name is
21 Bob Heflich. I'm from the FDA and NCTR, which is in
22 Arkansas. We're a research center for the FDA. We

1 have no regulatory role. We're strictly here to
2 advise and help the product centers. I've been FDA
3 employee since 1979, coming out of Veronica Maher's
4 ranch -- slides were given earlier in a talk.

5 And for the last six-plus years, I've
6 been director of the Division of Genetic and Molecular
7 Toxicology. Over the years, I've been involved in a
8 lot of in vivo mutagenesis-type studies seeking to
9 develop methods that could be used for -- to
10 compliment the in vivo (indiscernible) assays that are
11 generally used for in vivo assessment of gene tox
12 using a gene mutation influence.

13 The most commonly used today is the
14 transgenic rodent assay which appeared in the late
15 '80s and has developed into an assay over the '90s and
16 2013, I think, is the last OECD test guideline
17 version. More recently, I've been involved with
18 developing the PIG-A gene mutation assay and we're
19 currently engaged in trying to get a OECD test
20 guideline for that approved.

21 The other -- the major research
22 initiatives in the division are to explore the use of

1 error-corrected next generation sequencing for
2 evaluating sequence changes. I think that's -- this
3 has a great potential to revolutionize the practice of
4 genetic toxicology and perhaps we'll find usefulness
5 in regulatory applications.

6 The other thing we do a lot of is in
7 vitro tissue models, is a more of a risk
8 characterization tool for genetic toxicology, so I
9 think I'll stop there. Doug?

10 DR. DOUGLAS BRASH: Okay, thanks. My
11 name is Doug Brash. I'm basically a biophysicist --
12 I'm at Yale -- basically a biophysicist who ended up
13 working on how sunlight causes skin cancer. We
14 started out in some of the biophysical events looking
15 for the mutagenic photo products, back in the days
16 when we were just able to look -- use DNA sequencing-
17 like technologies to locate them and found out which
18 ones are mutagenic.

19 We found out that mutations aren't just
20 coming randomly from (indiscernible), and then we
21 started -- said somewhat foolishly, well, gee, can we
22 find the genes that are hit by sunlight causing -- in

1 order to cause skin cancer. And in retrospect,
2 amazingly enough, that worked and we found what came
3 to be called UV signature mutations (indiscernible) of
4 other genes in skin cancer.

5 And then, we started to worry about
6 (indiscernible) anyway and that got us into the
7 apoptosis story and (indiscernible) expansion that I
8 alluded to a little bit earlier. Lately, we've gone
9 into some unusual chemistry where UV (indiscernible)
10 will cause DNA damage, even in the dark for hours
11 after leaving the beach, so we're trying to follow
12 that up. It involved melanin.

13 We think it may be involved in other
14 diseases besides skin cancer, like you have melanin in
15 your brain, for example, and also we're trying to use
16 detection -- sequencing-based methods toward detecting
17 mutations in, right now, DNA photo products
18 (indiscernible) skin to get an objective measure of
19 what your past sunlight exposure is -- was, so that we
20 can maybe devise a measure of risk so we can tell
21 people, you should go see your dermatologist once a
22 year.

1 DR. ALAN BOOBIS: Good afternoon. I'm
2 Alan Boobis. I'm emeritus professor of toxicology,
3 Imperial College London.

4 I retired from my fulltime position a
5 year or so ago where I was at the postgraduate
6 research department of Imperial for 40 years as a
7 academic research worker and over that time, my
8 research has involved a variety of different
9 activities including mechanisms of toxicity and
10 carcinogenicity and the genetic toxicology of
11 polycyclic aromatic hydrocarbons (indiscernible) the
12 toxin both looking at in vitro, in vivo assays as a
13 means to an end, to try to understand the mechanisms
14 of activity and experimental models in humans.

15 The department I was in was a
16 department of experimental medicine in the medical
17 faculty, and as such, I have been exposed to medical
18 research for my entire academic career, which includes
19 conducting and participating in Phase 1 trials of new
20 drugs and also doing exposure of human volunteers to
21 radiation for experimental purposes.

22 In parallel, for the last 25 years or

1 so, I have been a member of national and international
2 scientific advisory committee, assessing the risk to
3 humans or potential risk to humans of a variety of
4 chemicals including (indiscernible) drugs, pesticides,
5 contaminants, and food additives and that has included
6 having to look at the toxicology, genetic toxicity,
7 and carcinogenicity of those compounds in both data-
8 rich and data-poor situations.

9 DR. TIMOTHY MCGOVERN: Good afternoon.
10 My name is Tim McGovern. I'm an associate director
11 for pharmacology, toxicology, (indiscernible) new
12 drugs in CDER. I'm not a genetic toxicologist by
13 training, by I know many people who are. Part of my
14 role, I sit on the Executive Carcinogenicity
15 Assessment Committee in CDER.

16 Also a member of the gene tox
17 subcommittee. I'm also a member of the ICH M7 working
18 group which is for DNA reactive impurities as well as
19 the S1 group looking at carcinogenicity assessment.

20 And also part of my work is working
21 with review divisions (indiscernible) when these
22 issues come up, where we get positive findings or

1 questionable findings in gene tox assays and making
2 that determination whether those findings rise up to
3 the level of warranting a clinical hold or not and
4 what possible followup studies may need to be
5 conducted to further evaluate the issue.

6 DR. MIRIAM POIRIER: Hi, I'm Miriam
7 Poirier. I started out my career doing animal
8 (indiscernible) studies in the laboratory of James and
9 Elizabeth Miller at the University of Wisconsin. For
10 something like 48 years, I was a paid employee of the
11 National Cancer Institute. I'm now an emeritus
12 employee -- that means I don't get paid.

13 But what -- the major part of my
14 career, we developed methodologies to measure DNA
15 adduct in human tissues and then we applied those
16 methods to look at the parameters of that information
17 in humans and to try and understand the mechanisms and
18 the consequences of DNA adduct formation in humans.

19 And -- oh, and I'm past president of
20 the Environmental Mutagenesis and Genomics Society.

21 DR. KEVIN PROHASKA: Thank you. I do
22 get paid. My name is Kevin Prohaska. I was

1 introduced earlier, obviously. Currently, I'm serving
2 as the FDA's senior bioethicist for adult research.
3 I'm the only ethicist for adult research, so that, by
4 default, makes me the senior guy, which is fine.
5 There are two other individuals who do the pediatric
6 research and as you can well imagine, more issues sort
7 of arise in research involving pediatrics, so there is
8 a need for two.

9 My background is -- I'm also board
10 certified in family medicine. I'm ex-U.S. military,
11 Army, and while I was with the Army I (indiscernible)
12 a lot of emergency medicine and so I was probably more
13 of an emergency room physician than a primary care
14 doctor, family practice doctor. Let the military.
15 Went into private practice.

16 Decided that it wasn't for me and then
17 I decided to come to the FDA where I started as a
18 primary reviewer in one of the review divisions in
19 neuropsych, which is now two different divisions,
20 neurology and psych department, and while I was there,
21 I was working on an awful lot of products including
22 ones related to bioterrorism which was right around

1 the time of 9/11 in 2001, which sort of stoked an
2 interest in (indiscernible) protections, so I started
3 getting involved in that, in some of the policy work
4 around that area and decided to pursue some experience
5 in bioethics and so I became over time the agency's
6 bioethicist.

7 In between all of that, I moved over to
8 the Office of Compliance where I was the director of
9 the Division of Safety and Investigation which I was
10 responsible for (indiscernible) oversight, radioactive
11 drug research committees, the post-marketing
12 pharmacovigilance program, and I'm forgetting the
13 (indiscernible) program.

14 So I have quite a few programs and I'm
15 doing (indiscernible) stuff. Thank you.

16 DR. ERROL ZEIGER: Hello. I'm Errol
17 Zeiger. I'm currently an independent consultant. I
18 started working in mutagenesis or genetic toxicology
19 at the FDA in 1969, before there was an Ames test, but
20 I was working with Ames' bacterial strains and doing
21 mostly testing and playing around with techniques
22 using bacteria, using yeast as good test organisms.

1 In 1976, I was recruited to go down to
2 the NIEHS to run a research lab and also to start a
3 testing program. Interestingly, in 1975, Bruce Ames
4 published a paper that, "Hair Dyes Are mutagenic."
5 For some reason, Congress picked up on it and in 1975,
6 '76, held budget hearings and directed NIEHS to start
7 a mutagenicity testing program to identify potential
8 carcinogens in the environment.

9 I was asked to design and develop it
10 and started up -- we started it up in 1979, the same
11 year that the National Toxicology Program started and
12 without my consent, against my wishes, we were taken
13 into the National Toxicology Program. So any NTP
14 detox studies you see now all came out of that
15 congressional hearing -- budget hearing, and initially
16 it was very well funded.

17 I asked for 12 slots; I got 12 slots.
18 So, but most of my career at NIEHS, from '76 until two
19 -- the end of 2000 was evaluating data, running the
20 test program, and publishing quite a few papers,
21 presenting the data, because this was before the
22 internet so we were actually presenting it in hard

1 paperback publications, and also evaluating the
2 effectiveness of different tests, alone and in
3 combination, for detecting carcinogens and for
4 complementarity.

5 I also spent over a year working with
6 OECD in Paris to look at, not so much gene tox but
7 other toxicology end points. And since then, since
8 2001, I've been an independent consultant in Chapel
9 Hill. Most of my consultations are related to genetic
10 toxicology (indiscernible) carcinogenicity.

11 DR. AISAR ATRAKCHI: Okay, thank you
12 very much for -- everyone. I appreciate you guys
13 coming back this afternoon as well as the start of a
14 very, hopefully, interesting discussion. So I would
15 like to start with the first question, which is really
16 the topic of this workshop and anyone who would like
17 to start addressing how many doses of an Ames-positive
18 DNA reactive drug can be safely administered to
19 healthy subjects, and in the sense that not -- these
20 are healthy subjects, so we should not, preferably,
21 change the cancer risk from one in a million as
22 opposed to in patients, we could accept 1 in 100,000.

1 DR. TIMOTHY MCGOVERN: I'll start out.
2 The -- one thing I wanted to bring up that was not
3 brought up this morning regarding scenarios where the
4 agency as well as other regulatory bodies already
5 allow exposure to mutagens by, in this particular
6 scenario, both patients as well as healthy volunteers
7 because under the ICH M7 guidance for DNA reactive
8 impurities and a threshold approach was developed
9 under that guidance, with a lot of work going on
10 before then where, essentially, for a long-term
11 exposure and a daily dose of up to 1.5 micrograms per
12 day is allowed without any further qualification data,
13 with exceptions of very high potency compounds like
14 nitrosamines.

15 And the guidance also works in a
16 stepwise approach as duration of exposure decreases
17 that that threshold will then increase to the
18 durations we're talking, possibly zero to five, maybe
19 up to 14-day exposure. ICH M7 has a threshold limit
20 of 120 micrograms per day for a one-month duration of
21 exposure.

22 And that level is associated with a one

1 in a million increased cancer risk. You could
2 continue that calculation (indiscernible) to even
3 shorter durations. If you're talking about a one-day
4 exposure, that would be the equivalent of 3.8
5 milligrams per day, still associated with one in a
6 million cancer risk.

7 So I just wanted to point out that we
8 do have scenarios in place. It's slightly different
9 than first in human, healthy volunteer trial, but for
10 impurities, yeah, we assume for the most part that
11 there's no inherent benefit being gained by the
12 presence of an impurity, the same way we're talking
13 about for a healthy volunteer trial, that there's no
14 inherent -- for the most part, inherent benefit for
15 healthy volunteers to be exposed to a mutagenic drug.

16 So you can make the argument, anyway,
17 that through surgery we've already made a case that
18 healthy volunteers can be exposed to mutagens and
19 questions really -- what level of that exposure do we
20 find acceptable. If we go with the 30-day cutoff for
21 M7, we're saying 120 micrograms per day.

22 Then obviously we'll put a fairly

1 limiting cap on those drug development programs
2 without further evaluation being done, but you can
3 also push that argument further and say, you have 3.8
4 milligrams per day for a single dose could also be
5 acceptable, except for very extreme cases.

6 So I just wanted to add that to the
7 case that was brought up earlier regarding microdosing
8 scenarios which allows up to 100 micrograms per day as
9 well.

10 DR. ERROL ZEIGER: Well, I would answer
11 that simply to say, it depends. It depends on the --
12 I would be interested in, not only, was it a mutagen
13 in vivo or in vitro, but what was the structure? Is
14 it something you expect to be highly DNA reactive? Is
15 it something that would be much less DNA reactive --
16 much less reactive?

17 And I can't separate out the concept
18 that we just had -- all of us had doses of mutagens at
19 lunch today: The soup, the broth -- chicken broth,
20 coffee for people that drink it. We all are doing it
21 in that background. And that's, obviously,
22 acceptable. But I just like keeping that in mind.

1 But as far as the rest goes, I think we
2 need to know more if it's just Ames positive, to take
3 -- to come up with a dose, have to know a lot more
4 about the chemical, maybe even something about the
5 volunteer.

6 DR. AISAR ATRAKCHI: I think we have to
7 make the distinction between what we eat and what can
8 be present in drugs. Eating, it's a personal choice.
9 You can eat as many smoked meats or coffees or roasted
10 things, but I think the risk is different for drugs.
11 The drugs, we have to take them. We have no choice.
12 So I think, in my mind, we have to be more protective
13 of the patients.

14 In this case, what we're discussing is
15 healthy volunteers, so clearly, we all know that on a
16 daily, on an hourly basis, we do inhale or drink or
17 eat these type of mutagens. But I think, really, the
18 emphasis is more the quality of a drug as well as, in
19 this case, the drug itself. Is it okay for people who
20 -- again, these are healthy volunteers?

21 They have absolutely no benefit of
22 taking that drug except to serve, perhaps, the PK --

1 to determine the PK of that drug in order to give it
2 next to patients. It's well taken, the point, but
3 again, I think your point earlier for the structure,
4 it's not just mutagenicity. You indicated that we do
5 also need to know little more information.

6 MAN 1: I was going to agree with that,
7 yes. You know, hopefully we all got something out of
8 our lunch including some nutrition, so there was some
9 benefit there. The numbers that Dr. McGovern just
10 mentioned are very helpful to understand, very useful
11 putting the risk in perspective.

12 But when you're evaluating the risk of
13 research, you have to take all the risks involved and
14 so that includes the risk that might be inherent in
15 the structure, unique things, but all the other things
16 that might occur during that clinical trial, so all of
17 that needs to be considered.

18 DR. ALAN BOOBIS: So I'm assuming when
19 we're trying to move away from a de minimis approach
20 like the threshold of toxicological concern, because
21 that is established. It's based on a large database
22 of genotoxic carcinogens, which is currently

1 undergoing refinement, but it's an approach that could
2 be used to find what is the maximum dose that's
3 associated, at worst, with (indiscernible). It's not
4 associated with one in a million. That's the worst
5 case because that's the extreme of the distribution.

6 But if we want to try and move the dose
7 up, it does depend, but I'm assuming that in the Phase
8 1 trial you don't have a in vivo tox followup on a
9 gene mutation assay.

10 DR. AISAR ATRAKCHI: Sometimes, some
11 companies will do that entire battery, but in general,
12 based on the guidance, we do not need to do that. You
13 only need the gene mutation to make the Ames test and
14 in vitro (indiscernible), generally.

15 DR. ALAN BOOBIS: Because if I had a
16 good in vivo gene mutation followup, not a
17 micronutrients test but I mean, actually looking at a
18 proper gene mutation assay in vivo and it was a
19 (indiscernible), my conclusion would be somewhat
20 different in -- even if (indiscernible) in vitro, than
21 if it was just an in vitro positive with no in vivo
22 followup.

1 That's the first thing. Second thing
2 is that not all adducts which cause mutations are
3 equal, so that we've got to think about the kinetics
4 and the dynamics, how reparable is the lesion which is
5 information we generally don't get. But you might be
6 able to (indiscernible) from the structure because we
7 know something about the reparability of seven types
8 of adults.

9 And the persistence of the compound
10 will determine how many doses or what duration. So
11 all that information would go into a weighted evidence
12 conclusion. I do not think there's a single answer to
13 this question.

14 DR. AISAR ATRAKCHI: I think -- so we
15 don't -- I'm loud. So we don't have the structural
16 similarity. These are -- so (indiscernible) a trial
17 that there's new molecular entities, we don't have
18 similarities to other structures for the point that
19 was initially discussed, so what happens when we don't
20 have any structural similarities that we can compare
21 it to something else because we have (indiscernible)
22 entity.

1 We don't have another data, either, so
2 we are just relying on Ames positive. That's all we
3 know. And there's no carcinogenicity data, either,
4 because we are so early on in the development that
5 such data are not available.

6 DR. ALAN BOOBIS: But you do know the
7 structure of the chemical.

8 DR. AISAR ATRAKCHI: We know the
9 structure --

10 DR. ALAN BOOBIS: So I'm not a
11 computational chemist, but I know the computational
12 chemist can tell us quite a bit about what a chemical
13 might do based on structure. And it's not based on
14 the entirety of the structure. It's based on
15 structural motifs. Which motif is -- confers on that
16 chemical Ames positivity?

17 And how reparable is that motif? A
18 compound that contains that motif, if I get an adduct
19 of a similar compound with the same (indiscernible).

20 DR. AISAR ATRAKCHI: Certainly, we get
21 this with M7. The M7, you do get the structure of the
22 QSAR (indiscernible), but I'm not sure we can or

1 should do this for an API, for a drug that is NME
2 that's coming in and it's already, we have a test.

3 DR. ALAN BOOBIS: No, I'm just --

4 DR. AISAR ATRAKCHI: The test is
5 telling us it's an Ames positive.

6 DR. ALAN BOOBIS: No, I'm not
7 suggesting you place the -- I would certainly never
8 suggest a computational approach should override a
9 biological test.

10 DR. AISAR ATRAKCHI: Okay.

11 DR. ALAN BOOBIS: I'm saying it adds to
12 the overall weight of evidence.

13 DR. AISAR ATRAKCHI: I see.

14 DR. ALAN BOOBIS: It helps you in your
15 interpretation of what might happen.

16 DR. AISAR ATRAKCHI: And that could be
17 very muddy, too, because you get on page back that it
18 could be this, it might be this, it might be that.

19 MAN 2: (indiscernible) can I just
20 pursue that for a moment? So Errol told us earlier
21 about a lack of correlation between mutagenic potency
22 and cancer potency, but now, it sounds like you're

1 going back to that and so the question is, has anybody
2 looked at that kind of QSAR or the kinds of adducts
3 and correlated that with cancer potency? Is there
4 data on that?

5 DR. ALAN BOOBIS: I'm not sure that
6 we've gone all the way out to cancer potency. I think
7 what they've done is looked at the persistence of
8 mutations in vivo.

9 DR. AISAR ATRAKCHI: Because, again, I
10 mean, we have to remember these are gene
11 (indiscernible), we use them as a (indiscernible), so
12 -- and they're mutagenicity (indiscernible). To take
13 them as far as predicting, extrapolating the potency
14 of a mutagenic to a carcinogenicity, it seems
15 inappropriate at this time. I don't think we have --
16 certainly as I hear you saying that it's a weight of
17 evidence and maybe that's what it comes down to.

18 MAN 3: I want to push back a little
19 bit and also be a little bit of a devil's advocate,
20 which I'm very good at sometimes, about this first
21 question about healthy subjects. It kind of defies
22 that. We're okay if it's patients. When, in fact,

1 one, two, three, or four doses is probably going to
2 have no beneficial effect on that patient
3 (indiscernible). Right?

4 So what makes the difference? Why do
5 we accept it for patients but not healthies because of
6 this -- neither one are going to be (indiscernible)
7 the efficacy of the drug? Is it just purely the
8 social aspect in that the patient, if this drug were
9 to be successful, will ultimately maybe benefit more
10 personally because they have the disease that would be
11 treated by that drug in the future?

12 Is that what makes the difference? And
13 is that enough to make that difference?

14 DR. KEVIN PROHASKA: I'm going to have
15 the review division helping me answering this, but in
16 part, I think part of it has to do with the fact that
17 there is a potential for benefit in some of these
18 circumstances when you have the condition, albeit, it
19 may be small, but the other thing to keep in mind is
20 you might be able to roll in from a Phase 1 right into
21 a Phase 2 with that same individual if there's -- some
22 good basic work has been done to be able to do that.

1 So there is some value in that
2 approach.

3 DR. ERROL ZEIGER: And you're also
4 going on the assumption that the patient with the
5 syndrome will handle, will mechanicalize the drug, the
6 drug will be similar response to a healthy person
7 because the drugs are not going to be given to a
8 healthy person. They'll be given to a person with the
9 syndrome, whatever you're trying to cure. And that's
10 the assumption that they will both respond similarly
11 to the drug.

12 DR. MIRIAM POIRIER: I don't think you
13 can answer this question the way it's written. It's
14 written, what can be given safely, one, two, three, or
15 four doses. I don't think there's any way of knowing
16 that. For most new compounds that you see that
17 (indiscernible) and you have some basic information,
18 but if you look at the (indiscernible) paper and then
19 what you all have done and then (indiscernible) to
20 follow up on that, I mean, I don't think that we can,
21 in good conscience, ignore 60, 70 years' worth of
22 tumor studies.

1 And even if some -- you can make
2 arguments that some of those studies weren't perfect,
3 the weight of evidence, I think, with your paper and
4 with what came before you is that there is -- there
5 are many, many cases in which one dose or a low dose
6 or a single dose has produced cancer.

7 So we can go ahead and give these drugs
8 and make our best estimates of what's going to be
9 safe, but I honestly think in the light of the
10 evidence that's out there, you can never really say
11 that something is going to be safe. And, bottom line
12 is, you don't have the end of that experiment because
13 that person is probably going to be a young person.

14 They're going to go on and reach 70 or
15 80 and maybe they're going to get cancer, maybe they
16 aren't, but you're never going to know where that
17 cancer came from. And so there is no way of answering
18 this question as it's written, I believe.

19 DR. ROBERT HEFLICH: So I get the
20 impression that you're hesitant as for additional
21 information when this comes up.

22 DR. AISAR ATRAKCHI: No, it's not the

1 hesitation. We get the implication from a sponsor
2 with a -- they just want to do the (indiscernible) and
3 a single dose, maybe up to 14 days of an NME, new
4 molecular entity. They've done -- all the guidances
5 that we have out there in terms of the mutagenicity.
6 They have -- sometimes, they have 14-day tox study,
7 (indiscernible) toxicology study (indiscernible),
8 maybe up to a month, maybe, and that's all we have,
9 and some other information in clinical. And the non-
10 clinical will determine what is the first dose that
11 potentially is safe that can be administered. So we
12 really -- that's all we have and that -- and they're
13 following what we're telling them to do.

14 DR. ROBERT HEFLICH: Can you just say
15 stop, we can't go any further with this?

16 DR. AISAR ATRAKCHI: We can.

17 DR. ROBERT HEFLICH: Because it's a
18 mutagen and you need to give us X, Y, Z before you can
19 go --

20 DR. AISAR ATRAKCHI: Yes, we can, for -
21 - I mean, again, I think most of you know, or if you
22 don't know, it is rare that we get an Ames positive

1 drug from Phase 1. I've been here 27-plus years.
2 Only once I've seen that happen and we put that drug
3 on hold. So reality is we don't -- we're not faced
4 with this all the time, but we do -- you could get an
5 equivocal response, but it's still slightly positive
6 in Ames.

7 DR. ROBERT HEFLICH: Well, maybe if you
8 had a path forward, you would see more of this.

9 DR. AISAR ATRAKCHI: Meaning -- path
10 forward what?

11 DR. ROBERT HEFLICH: If, you know, the
12 drug turned out to be Ames positive and you had a
13 followup that you could recommend to the company, the
14 company might be more willing to put such a drug
15 forward as an IND.

16 DR. AISAR ATRAKCHI: Well, but I think
17 what the issues is some of us who, if we see such a
18 drug, we will say, but it's only -- they're doing one
19 dose in the healthy volunteers. I think it's okay
20 because, let's say, the (indiscernible) was negative.
21 Others will say, no, this is a positive Ames. I'm not
22 going to let you go, but you need to give me more

1 information.

2 Others will say, but two or three
3 doses, it's okay. So this is why we're asking this
4 question and we -- I mean, that's why we're trying to
5 get from you --

6 DR. ROBERT HEFLICH: I think every --

7 DR. AISAR ATRAKCHI: (indiscernible).

8 DR. ROBERT HEFLICH: Everyone here
9 would say it's unknowable.

10 DR. AISAR ATRAKCHI: Is what?

11 DR. ROBERT HEFLICH: It's unknowable.
12 You can't give an answer to that based on what we
13 know. It requires more information. I mean, there's
14 lots of examples where single doses produce tumors, in
15 both humans and animals.

16 DR. AISAR ATRAKCHI: And we could see
17 that today, we have -- from the presentation --

18 DR. ROBERT HEFLICH: So in other words,
19 if you had a followup test in vivo gene mutations test
20 that was negative by statistical criteria that you can
21 set, would that be sufficient to say the Ames test is
22 not significant for in vivo effects?

1 DR. AISAR ATRAKCHI: That is a question
2 later on, so we're starting here, then we can move --

3 DR. ROBERT HEFLICH: Well, maybe --

4 DR. AISAR ATRAKCHI: Because we want --
5 so I think what I'm -- Todd, would you like -- let's
6 hear your question and then we can...

7 TODD: It was just a comment that the
8 examples that we saw today, those are pretty well
9 recognized mutagenic genotoxic agents, and to your
10 point, what we're most likely to deal with is
11 equivocal things where we have a mixed profile with a
12 standard battery.

13 It's not like the things that we were
14 seeing earlier today, so one, two, or three, four
15 doses may be if we reword it to say, it can be
16 reasonably safely administered, is probably a more
17 accurate way of saying it. If you really think about
18 it, I mean, at least in our division, we do healthy
19 subject (indiscernible) trials all the time.

20 With -- and there are toxicities,
21 minimal amount reversible and monitorable, that we
22 allow them to go to in healthy people. Is that risk

1 any different than if this was an (indiscernible)
2 toxic drug, when, let's say it's a renal toxicant,
3 right? You can monitor for that, you let them come up
4 to a certain level but not higher to avoid brain
5 toxicity.

6 That's a lot more of immediate
7 potential toxicity than cancer 40 years after that
8 single dose of (indiscernible) toxic drug. So it
9 seems like, I don't know, maybe our priorities there
10 in terms of assessing that risk is a little backwards.
11 The difference, though, is we monitor for these non-
12 genotoxic sort of toxicity, so we're able to do that,
13 typically. And error correct the sequence and maybe
14 reassert potential there for us to do, take blood
15 tests and look for mutational frequency in order
16 [OVERLAPPING SPEAKERS]. I'm sorry?

17 DR. AISAR ATRAKCHI: And people?

18 TODD: Yeah, and people. I know
19 companies will not like to do that.

20 DR. AISAR ATRAKCHI: They can't, you
21 know [OVERLAPPING SPEAKERS] but, ethically, we cannot
22 do that. That's a lot of reasons that companies would

1 not do that.

2 TODD: I think we can make that -- we
3 can argue the evidence of it, but let's forget people.
4 What about (indiscernible).

5 DR. ERROL ZEIGER: Okay, if there's one
6 thing we know about Ames and in vitro mammalian cell
7 (indiscernible). They are tremendously imperfect
8 predictors of potency in cancer. So, say we got
9 something equivocal in the Ames test really is not
10 necessarily put your mind at ease that this is only
11 marginal.

12 Of course, it could be -- because it
13 may be part of particular activation pathway that's
14 not represented in the S9 that's used in the standard
15 Ames test. It could be a lot of reasons why you get a
16 weak response. So I don't think you can necessarily
17 equate an equivocal in vitro assay with a lack of
18 risk.

19 TODD: Well, when I say equivocal, it's
20 (indiscernible) that with more than just the one test.
21 We have several tests and it might give us marginal
22 positives, one, maybe (indiscernible) another -- but I

1 understand.

2 DR. AISAR ATRAKCHI: So, I think --
3 well, Dr. Brach, you didn't say -- I'd like to hear
4 from every person on the panel, so would you like to
5 add to this in any way?

6 DR. ROBERT HEFLICH: (indiscernible).
7 Yeah, I do have a couple of thoughts. So one is,
8 basically, you don't know and at some point have to
9 say, oh, I don't know. And another one is -- a
10 thought that had occurred to me (indiscernible) other
11 times is, okay, so if you gave low doses over several
12 times so that you had this washout period, not just
13 for the drug but time for repair, that maybe you could
14 talk me into it, but you don't know that until you
15 (indiscernible).

16 And, that brings me to the third point
17 which is, who's the normal volunteer here and the --
18 an exam question when I was at school was what's wrong
19 with the phrase, "You have the wrong number," and the
20 answer is, "the."

21 So there's lots of wrong numbers and
22 there's lots of normal volunteers and so you have all

1 (indiscernible) to deal with and even -- if the
2 patient has an inflammatory condition or something you
3 didn't know about or is the drug going to be hitting
4 at the same time the liver cells decided to divide?
5 You don't know any of this.

6 And so the only, I guess, coherent
7 thought to put all this together is that only
8 (indiscernible) test in light of the presentations
9 about single doses, low doses, is that the existing
10 data isn't enough to reassure me that a small number
11 of low doses (indiscernible).

12 DR. AISAR ATRAKCHI: I think if I -- to
13 summarize for question one is that there is no one
14 answer, which we kind of knew that, but weight of
15 evidence and also you -- if you saw a clear dose
16 responsive, positive Ames of a drug, you would not or
17 would you still say, for a single dose in humans I
18 would give it? I think that's really what we're
19 trying to understand.

20 Now, again, we -- like was mentioned,
21 you do have chromosomal aberration test and it's
22 negative. This structure -- I mean, I think what I've

1 heard is that it's the weight of evidence. Everything
2 about that particular molecule. But if you have an
3 Ames -- clear Ames positive dose response and the
4 sponsor repeated it and it's positive, maybe their
5 dose -- the concentration, they narrowed it down. It
6 was too large and they narrowed it down and it's still
7 positive.

8 We don't see the (indiscernible) there.
9 But just if we do and we're not talking about
10 equivocal, would you allow such drug to be tested in
11 healthy people?

12 DR. ROBERT HEFLICH: You're turning
13 this into, certainly, an Ames test interpretation.

14 DR. AISAR ATRAKCHI: I am, because
15 that's what we get.

16 DR. ROBERT HEFLICH: We know from a
17 number of different compilations that a positive Ames
18 test, if you're looking just across chemical
19 structures, there's about 70 to 80 percent predictive
20 of rodent carcinogenicity as either ra or mouse, not
21 necessarily both. Whether it's a strong Ames test
22 positive or a weak Ames test positive, it's positive

1 and the date showed -- you look at the data, the TD50s
2 and the Ames test, the potencies, there is absolutely
3 no correlation.

4 We did a study -- I did a study about
5 10 years ago using 100 chemicals that were Ames test
6 positive in the NTP. They're looking at the slopes
7 and lowest (indiscernible) TD50 values for the same
8 chemicals. The correlation was 0.04-something. Not
9 the P value, the correlation. It looked like a
10 shotgun pattern from about 10 paces.

11 So where there are some -- where the
12 Ames potency is 1 microgram -- mutation per microgram
13 or 10,000 mutations per microgram, it's not going to
14 make any difference as to whether or not you should be
15 more or less concerned about that response.

16 DR. ALAN BOOBIS: I think that's right.
17 I think it's a positive ID and I would really feel
18 very uncomfortable giving a clear Ames positive unless
19 I had some reason to strongly think that this is just
20 an artifact of the assay and there would be a
21 dispositive indicator. There are compounds that we
22 know will give a (indiscernible) positive.

1 We also know they're going to be
2 (indiscernible) because it's very difficult to make
3 that case in the absence of the (indiscernible). So
4 in general, the question -- the answer would be not
5 unless there's really good reason to come to a
6 different conclusion.

7 DR. TIMOTHY MCGOVERN: So, I mean, you
8 can get a reproducible dose response for -- in TA100
9 for phenobarbital, which is a little carcinogen but
10 almost certainly not a mutagenic (indiscernible)
11 carcinogen. So perhaps the way to ask question one is
12 not, can you give it for one, two, three, or four
13 doses, but what would you need to know about a drug to
14 feel comfortable giving it for a small number of doses
15 to a healthy volunteer.

16 And the other thing to keep in mind is
17 that you're really making two decisions here, not just
18 one. Because after you finish your Phase 1 trial,
19 you're probably not going to have a whole lot of more
20 pre-clinical information about the drug and you're
21 going to have to start deciding, are you going to give
22 this drug to patient volunteers in Phase 2.

1 And so you're going to have to inform
2 them of their risk of cancer from this mutagenic drug
3 and so unless you're thinking ahead to that and what
4 you're going to need to know to answer that question,
5 because presumably most drugs make it through Phase 1,
6 there's really a bar -- that way if the problems come
7 up, problems come up in Phase 2 so you're also going
8 to be giving more doses of that drug to patient
9 volunteers.

10 DR. ROBERT HEFLICH: I think as part of
11 that calculation, what we typically -- this narrative
12 came up with the person (indiscernible) clinical trial
13 being proposed, the division might say one dose okay,
14 two sometimes four okay, but then it becomes a partial
15 clinical, before you go any further you're going to
16 need to provide this additional information to clarify
17 or to address our concern regarding the positive Ames
18 finding.

19 DR. TIMOTHY MCGOVERN: And maybe the
20 answer is if you do that, work as one, you can go into
21 it as one. So if you've already worked out that
22 scenario for going into Phase 2, then maybe those are

1 the kinds of -- who was it, Bob, talked about case
2 studies -- case studies. You know, maybe you can look
3 at some of those case studies of drugs that were Ames
4 positive and you had to make that decision for Phase 2
5 and what made you feel comfortable about the safety in
6 Phase 2.

7 In some ways, I would say, okay, it's
8 two. Patient is more vulnerable than a healthy
9 volunteer because the Phase 2 patient is being
10 motivated by getting a drug that may or may not
11 benefit them.

12 DR. AISAR ATRAKCHI: Okay, any other --

13 DR. ERROL ZEIGER: Another thing about
14 this is we're talking as if the Ames test data is
15 written into law. Regulations can change. There's
16 nothing to stop FDA from looking at the situation
17 saying before you -- if you have a positive Ames, we
18 want this additional information before we'll approve
19 any clinical trials. That's the function of FDA's
20 ability, not Congress or anybody else.

21 DR. AISAR ATRAKCHI: No, absolutely,
22 but I mean you don't want to -- it hasn't been even

1 administered to, (indiscernible) first to anyone, so
2 potentially that drug that was developed by the
3 company, presumably, will have some benefit down the
4 road. So we don't want to stop that and ask for a lot
5 more information if -- unless, of course, we feel the
6 need for that, we're not convinced with the
7 information.

8 We think this is real finding, real
9 toxicity. I mean, certainly, like Todd was
10 mentioning, it's not only mutagenicity. If we have,
11 in my division, if we have a variety of causes, brain
12 lesions or cause -- brain lesion in the rat in a 14-
13 day study, we are not allowing that rat to unless we
14 have one mechanistic understanding. They need to do a
15 lot more to show us that that finding either is
16 reversible or it's not (indiscernible). So it's not
17 just mutagenetic.

18 DR. ERROL ZEIGER: Yeah, but the
19 discussion, as it's being directed, is strictly
20 towards mutagenicity now. We're being asked to
21 address the question, if we only have a positive Ames
22 test. So, granted, you're talking about 14-day

1 studies. Ideal. You're not going to know from an
2 Ames test if you're going to get kidney lesions or
3 brain lesions or anything else, unless you've got a
4 structural similarity to known bad actor drugs. So
5 you just changed the question on us.

6 DR. TIMOTHY MCGOVERN: No, but I think
7 what you're -- obviously, it's not written -- I agree,
8 it's not written in stone. We can ask for additional
9 information. But what we're looking to get input on
10 is, when do we need to get that additional
11 information? Can we wait until -- can we say, okay,
12 single dose does not represent a significant risk to
13 the patient, and get that information later or do we
14 need it before we go and do healthy volunteer dosing
15 at all?

16 DR. ERROL ZEIGER: I think part of the
17 answer to the question is, so you're saying that maybe
18 we shouldn't consider four, three, or two doses, only
19 a single dose and then make a secondary decision.

20 DR. TIMOTHY MCGOVERN: I mean, it could
21 be -- I mean, that's what was presented earlier is
22 that some divisions allow the single dose and then ask

1 for additional information. Some divisions have been
2 asking or allowing two doses and then in some more
3 limited scenarios allowing up to four doses. That's
4 where one, two, and four are coming from.

5 So it's really trying to get input from
6 the panel as to, does one represent a significant risk
7 or some number larger than one represent that risk and
8 at what point should we really be asking for that
9 followup information before making that decision --

10 DR. ERROL ZEIGER: And maybe the answer
11 is, no dose [OVERLAPPING SPEAKERS] decide what
12 significant risk is. If four gives you a risk,
13 significant risk, does one give you one quarter of
14 that risk?

15 TODD: I'm trying to remember what I
16 was going to say. There was a time when I first
17 joined FDA about eight years ago that if a drug came
18 in (indiscernible) drugs that we look at or oversee
19 are -- obviously, diabetes, endocrine related
20 indications.

21 If there was any question, there was --
22 it was Ames positive, whether it's a blip or extreme

1 positive or just a mixed picture from the
2 (indiscernible) profile, it'll go on hold without
3 dosing, pending the results of the six-month
4 transgenic study. And then it would be released from
5 hold if there are no tumors and they go on with their
6 lives.

7 It's very uncommon that we would see
8 that situation anyway, but I'm wondering, does
9 (indiscernible) to go back to that sort of paradigm or
10 is the relationship between a positive outcome and a
11 transgenic and a mutagenic or something that's
12 clinically genotoxic or truly genotoxic? Is the
13 connection that strong where we're not going to get
14 falsely assured by a negative transgenic?

15 I'm always worried about that, so if
16 it's a negative transgenic, go ahead. But is that
17 really speaking to the cancer risk of whatever
18 mechanism we're worried about in the beginning?
19 Should we move back to that? I mean, the other
20 element, of course, is from a very practical point of
21 view, some -- if a sponsor comes in for developing a
22 diabetes drug, if we have a question about its

1 genotoxicity, no, we're probably not going to let it
2 go anywhere because we're just going to tell them to
3 start over.

4 We don't need -- it's not exactly an
5 unmet medical need, so I assume that the cases,
6 scenarios are being discussed here, there's a clinical
7 need for testing these drugs because otherwise why
8 even bother? It's a non-starter.

9 DR. AISAR ATRAKCHI: Right, I mean,
10 certainly we will -- as you know, we will weigh the
11 risk versus the benefit. If this is -- like you said,
12 if this is just another diabetes drug or it's another
13 sleep drug but it shows this equivocal or even a
14 positive Ames, we certainly -- likely we will ask for
15 followup. Go tell us why this is positive.

16 But the question about what would you
17 follow it up with, whether it's in vivo transgenic or
18 something else, that's going to come up in the third
19 or fourth question.

20 TODD: Okay.

21 DR. AISAR ATRAKCHI: But right now, I
22 think since it looks like it's a weight of evidence

1 more or less, if it's -- we can summarize this, maybe,
2 a little later, but that's why I said, the second
3 question relates to the first one which is, if we are
4 to allow this mutagenic DNA reactive drug to be
5 administered to healthy subjects, would you allow this
6 drug to be given continuously, meaning daily, or -- if
7 so, for how long, how many days? Is 14 days, 10 days?
8 Or if not, then would you allow to give it
9 intermittently, let's say, with a washout period of,
10 as mentioned earlier, you have five half-lives, so
11 that the drug will be cleared and then you get a
12 second dose.

13 DR. BOB BRASH: On the intermittent
14 issue, I'd like to see Paul Brown come up here.

15 DR. AISAR ATRAKCHI: Well, we're going
16 to hear --

17 DR. BOB BRASH: -- put you on the spot.

18 DR. AISAR ATRAKCHI: -- from the panel
19 to see what they think and we'll move on to your
20 questions.

21 DR. MIRIAM POIRIER: So I wanted to
22 talk about dosimetry. Phase 1 clinical trials are for

1 determining toxicity, right? And they're often
2 escalated, so mean, the dose makes the poison, so, I
3 mean, we talked about 1.5 micrograms or 3 milligrams.
4 What -- different doses -- different drugs probably
5 need different doses for efficacy and to hit the toxic
6 limit, so seems to me that the dosimetry should be
7 somewhere in the calculation.

8 And I also wanted to bring up the third
9 rail, which is human monitoring. I mean, as -- nobody
10 wants to do it, I guess, but along with -- I mean, the
11 safe harbor that we had in the past and everybody was
12 afraid of looking at transcription that would be very
13 sensitive and it turns out it's not, hey, we could
14 learn and healthy volunteers probably wouldn't mind
15 giving some blood or urine.

16 We'd find out what -- a lot about
17 what's going on in humans that we can't otherwise
18 determine just by -- we have the technology. It's
19 there and it's improving, so I think we should at least
20 consider it in the context of understanding what a new
21 drug might be doing in humans, and in different humans
22 with different metabolic capabilities.

1 DR. AISAR ATRAKCHI: So, can we move on
2 to the second question?

3 DR. MIRIAM POIRIER: Oh, you wanted
4 (indiscernible).

5 DR. AISAR ATRAKCHI: Sure.

6 DR. ROBERT HEFLICH: I like what you
7 said, (indiscernible), because I think there is a role
8 for human monitoring because we're going to make the
9 decisions based on surrogate systems, rodents, and
10 we're going to say okay, this positive Ames is
11 mitigated by a negative in rodents in the cancer or --
12 transgenic cancer assay or a gene mutation assay.

13 But the question remains, there's a
14 reason for that and it's probably related to
15 inactivation of the chemical by some pathway or repair
16 or something, but does the same thing happen in
17 humans.

18 And, of course, this is not necessarily
19 important to the healthy volunteers, but it could be
20 healthy to Phase 2 and Phase 3 individuals if you get
21 a surprise and the same thing doesn't happen in humans
22 and you can, perhaps, determine that by, if you go

1 ahead with this drug, finding out whether there's a
2 genetic toxicology signal in these volunteers that
3 take this drug. Just a thought.

4 DR. AISAR ATRAKCHI: So I think we
5 should move on to the second question, which I'm
6 guessing is you may move fast, because we already have
7 discussed some of it and the first question, so would
8 anyone like to start with the Part A of the panel?

9 Would you give it for, I guess -- it's
10 the same thing as we've been discussing if -- a lot of
11 things to consider in order to give it, but I think it
12 would be helpful if we can hear from you whether,
13 would you give it on a daily basis for a short period
14 of time or would you simply say, no, because of the
15 results of the mutagenicity, let's just -- and maybe
16 some other toxicology findings, that we're going to do
17 it maybe twice or wait -- give a dose and then wait
18 for five half-lives and then give it again?

19 Yes, please.

20 DR. ALAN BOOBIS: So assuming that the
21 decisions we take (indiscernible) possible
22 (indiscernible) in these Phase 1 studies --

1 DR. AISAR ATRAKCHI: Sure.

2 DR. ALAN BOOBIS: I think a starting
3 point would be simply to fractionate the dose. I
4 would argue Haber's rule and say that worst case --
5 potential worst case based on information we heard
6 this morning as well, the really -- if you think you
7 can give a single dose of X, then if you're going to
8 give it, basically for multiple doses, it should be
9 the appropriate fraction of those doses, unless
10 they're going to be so widely separated in time that
11 you could think they're separate, single doses.

12 DR. ROBERT HEFLICH: But for a PK stud,
13 you wouldn't fractionate the dose, would you?

14 DR. MIRIAM POIRIER: You can have -- in
15 general, it's a single ascending dose or it's once a
16 day for maximum 14 days. That maximum -- Phase 1,
17 more than 14 days, at least not in my division. So it
18 can be on a daily basis for up to 14 days, but it's
19 usually ascending. And it depends on the -- recently,
20 we've been having drugs that are given only once a
21 month, so maybe that is it. It's only one dose
22 because they have a very long half-life, so you're not

1 going to wait for -- if the half-life is one week,
2 you're not going to wait for four weeks in healthy
3 volunteers to do the other one.

4 DR. ROBERT HEFLICH: But when you say a
5 fractionated dose, you're comparing one good dose --

6 DR. ALAN BOOBIS: -- smaller dose.

7 DR. ROBERT HEFLICH: -- smaller doses
8 that add up to that one big dose.

9 DR. ALAN BOOBIS: Yeah.

10 DR. ROBERT HEFLICH: But you'd never do
11 a study like that, would you, for a PK study. Would
12 you do an experiment like that?

13 DR. AISAR ATRAKCHI: (indiscernible).

14 DR. ERROL ZEIGER: Going along with
15 this, if you're going along with (indiscernible), my
16 first question would be, why are you doing this study.
17 What questions are you -- specific questions are you
18 asking?

19 DR. AISAR ATRAKCHI: Oh --

20 DR. ERROL ZEIGER: Is this going to be
21 looking at clinical side? Are you going to be looking
22 at --

1 DR. AISAR ATRAKCHI: This is a clinical
2 PK, usually, and to determine what's the maximum
3 tolerated dose in people.

4 DR. ERROL ZEIGER: In other words --

5 DR. AISAR ATRAKCHI: So the
6 (indiscernible) dose for the patients.

7 DR. ERROL ZEIGER: You're looking for -
8 - for a clinical size.

9 DR. AISAR ATRAKCHI: Yes, and a form of
10 the kinetics and what dose will be the most
11 appropriate dose to use for Phase 2 in patients.

12 WOMAN 1: (indiscernible) based on
13 (indiscernible).

14 DR. AISAR ATRAKCHI: I mean, it's the
15 PK.

16 WOMAN 2: -- not for the human side,
17 but also in Phase 2 (indiscernible) the PK study
18 (indiscernible) somehow we can (indiscernible)
19 multiple doses, so (indiscernible) so it's really not
20 that simple. (indiscernible) in vivo, and we cannot
21 really -- for oncology patients, we cannot draw on
22 that because patient have a lot of comorbidities.

1 We cannot -- so that's a rarity we
2 have, (indiscernible) level. Even we have
3 (indiscernible) study to provide this information,
4 otherwise the (indiscernible) information.
5 (indiscernible).

6 DR. ALAN BOOBIS: I think it's going to
7 be easier to do a single dose PK study than to do a
8 full Phase 1 study with -- looking for maximum dose
9 with a (indiscernible).

10 MAN 4: One of the reasons to do the
11 study is a food effect study under fasted and fed
12 conditions, so that you like to use the same patients
13 and -- the same subjects and give them two doses,
14 maybe spread a couple weeks apart and it reduces the
15 variability of the study.

16 Another one is the bioequivalent study
17 that Bob Dorsam talked about today. It's better to do
18 these studies in healthy volunteers. You reduce the
19 variability and if you're using patients making a lot
20 of -- the underlying disease may really affect the
21 data that you get. So that's why this one dose versus
22 two doses is important to us, is that impacts the

1 study design. Do you do -- for, like, the food effect
2 study.

3 DR. AISAR ATRAKCHI: I don't know, I
4 think you -- I'm sorry, go ahead.

5 DR. MIRIAM POIRIER: No, I was going to
6 say, it seems to me that sequence, the first thing you
7 need to know is what your PK is because then if you're
8 going to have a washout period, you need to know what
9 that is, so (indiscernible) your PK and then take it
10 from there and decide on your second dose or whatever
11 you're going to do, but I think it has to be in a
12 specific order and sequence if it's going to make
13 sense.

14 PAUL BROWN: Paul Brown, CDER. Since
15 Bob told me to say something -- this issue about the
16 intermittent versus not intermittent, presumably
17 intermittent means for that space (indiscernible)
18 doses of, whatever, two weeks or something.

19 I mean, if we believe Dr. Brash's, what
20 is it, cancer cell loop (indiscernible) hypothesis,
21 then I'm not sure intermittent is any safer than doses
22 right next to each other and you could also come up

1 with a hypothesis that maybe intermittent is actually
2 less safe because now, you're fixing mutations and
3 then you -- in the second dose, you now cause a
4 mutation in that exact same cell.

5 You get that second hit and you build
6 them up over time rather than killing them all off
7 with your dosage right at once, so I mean, it's an
8 interesting thing to think about. I think we think
9 about it for other toxicities, right, where you do
10 recover from them. Okay, you can separate the doses,
11 recover from that tox, but maybe it's a little
12 different issue here.

13 The other -- I think the other point
14 that was made about dose is important. I mean, as Tim
15 pointed out, we're already doing this. We already
16 accept mutagenic compounds in health subjects. It's
17 the impurities. Now, they're very low levels. But if
18 we just think it's a hazard (indiscernible), why do we
19 do that? Obviously, we think there is a dose
20 response, that there is -- you know, (indiscernible)
21 with a straight line, whether that's right or not,
22 with risk and dose and so on, so can we come up with a

1 dose that's low enough that we'd be okay regardless
2 (indiscernible) TTC?

3 It probably isn't going to be a useful
4 dose in most PK studies. The reason to have the
5 microdose studies is because there are sensitive
6 assays now for looking at PK. Sometimes they can do
7 the microdoses and get those answers.

8 DR. AISAR ATRAKCHI: But didn't you,
9 Paul, with the impurity doing the QSAR as M7 clearly
10 says, up to 1 milligram, you can do all of these. So
11 once the impurity is above 1 milligram, then they're
12 going to go to (indiscernible) where they have to do
13 general tox study. They have to do the chromosomal
14 abrasion and so forth, with other caveats in there.

15 So I think, like we have discussed
16 internally, it's really the level of comfort with an
17 impurity versus an API. We're okay with the impurity
18 for a QSAR and not doing the test, but we're not that
19 comfortable when you're getting the drug in milligram
20 -- at least a milligram dosing. So I think there's a
21 little bit of a distinction and that underlines the
22 reason for M7 does not apply to APIs.

1 PAUL BROWN: Although, if you add the
2 same doses --

3 DR. AISAR ATRAKCHI: Right.

4 PAUL BROWN: I mean, if anything, you'd
5 be okay with the API.

6 DR. AISAR ATRAKCHI: Exactly.

7 PAUL BROWN: In a higher dose. Yeah.

8 DR. ALAN BOOBIS: But just to be clear,
9 the (indiscernible) toxicological (indiscernible) of
10 1.5 is based on cancer data not gene toxicity. In
11 other words, what he says is, if I've got a compound I
12 suspect, I know, is an Ames positive, I -- we will be
13 at this end of the distribution of carcinogens in
14 potency. And so it can permit up to 1.5 micrograms
15 per day with a reasonable assurance that
16 (indiscernible) over one in a million risk.

17 So it's not based on gene tox potency.
18 And I made that point because several groups,
19 including Health Canada are trying to find a surrogate
20 for the cancer (indiscernible) data in gene tox assays
21 and as Errol has pointed out, what we know is the Ames
22 test is not the answer and they're looking at various

1 in vitro and in vivo assays.

2 They think they're (indiscernible) an
3 in vivo assay. There might be a suitable surrogate
4 for that purpose. We don't know what the distribution
5 of the values is, so we don't know where the TDC would
6 be if you base it on a gene tox end point, but it will
7 probably be -- you could probably get away with a more
8 potent compound than for the carcinogens.

9 DR. TIMOTHY MCGOVERN: Yeah, I think at
10 this point when -- especially first in human trial,
11 we're using the Ames as a (indiscernible) predictor
12 for carcinogens, if we get to a point where we had a
13 marker from an Ames assay to give us a reasonable
14 estimated carcinogenic potency, that would be great.

15 Then we can go at it in a more educated
16 way, but unfortunately, now we assume it's a
17 carcinogen if it's Ames positive until shown otherwise
18 and it's really, what further -- is that okay for one,
19 two, et cetera dose and, as Paul was saying, at what -
20 - how high a dose can we give, as well.

21 DR. AISAR ATRAKCHI: So any further
22 discussion on -- I think we got that there is not

1 plans -- if I can summarize, I don't think there was -
2 - there is any summary of this, whether you can give
3 it continuously, daily, for an Ames positive. I heard
4 that it's better if you break it down, to fractionate
5 the dose, but again, it's similar to the microdosing.

6 When you give the drug that it's a new
7 molecular entity at a microdose, that's a below the
8 pharmacologic effect. So I'm not sure how valuable
9 that, which may be that's the reason we have not see
10 many companies coming in with microdosing clinical
11 trials. So from a practical point of view, I'm not
12 sure that would work.

13 So I'm not sure we got an answer to
14 this, but maybe it relates to the first question, that
15 it's all a weight of evidence type of thing. But I
16 did hear from Mr. Boobis that if it's a clear
17 positive, you will not like to see that drug
18 administered.

19 DR. ALAN BOOBIS: Unless there's a very
20 good argument.

21 DR. AISAR ATRAKCHI: Unless there is
22 very good argument, which is, actually, the opinion of

1 Health Canada based on our assessment of how they do
2 things. They do need -- if it's clearly Ames
3 positive, they will not allow that drug to proceed
4 unless it has some followup studies in vivo that shows
5 it's irrelevant, the finding.

6 So I think let's move on to the third
7 question. So now we're -- for generic drugs. As you
8 may know, they already have -- they usually reference
9 to the drug that's already approved, the innovator
10 drug, which they follow the label. There is a full
11 battery, generally speaking, of the gene mutations as
12 then there's a (indiscernible) study, if the drug is
13 administered chronically.

14 So they have this information already.
15 So they're -- but they still need, in order to develop
16 a generic drug, they still need to do a bioequivalent
17 study in healthy people to show that the innovator and
18 their -- and the generic drug have similar or
19 comparable (indiscernible) PK data.

20 So the question becomes, should
21 (indiscernible) evidence a product be used to decide
22 whether a compound should be tested in a bioequivalent

1 study in health subjects? If yes -- and again, this
2 is assuming that it's in the label, it says it's a
3 mutagen.

4 Already we know, and presumably we're
5 talking, again, about the gene -- about the mutation,
6 Ames test plus the other tests, the full battery; if
7 yes, which test results should receive greatest
8 consideration and the weight of evidence? Are there
9 any other factors relating to genetic tox that should
10 be considered when determining if that study should
11 include healthy subjects and bioequivalent studies?

12 And I open it for discussion.

13 WOMAN 3: How long are the
14 bioequivalent studies?

15 DR. AISAR ATRAKCHI: Couple weeks, max.
16 same thing.

17 DR. BOB DORSAM: (indiscernible) say
18 around four doses. It's within that range.

19 DR. AISAR ATRAKCHI: Okay. So --

20 DR. BOB DORSAM: There are others where
21 (indiscernible) focus on something (indiscernible).

22 DR. AISAR ATRAKCHI: So it's a simple -

1 - it's four doses, 14 days. Yes. Could be continuous
2 or not. Anyone from the panel, please. Dr. Boobis.

3 DR. ALAN BOOBIS: Yes is the answer to
4 Part A, one, before Part A. Should weighted evidence
5 of course be used? I think yes.

6 If yes, which test results would
7 receive greatest consideration? I would argue that
8 the appropriate followup for the in vitro positive, so
9 if it's in vitro Ames test positive, you need -- you
10 would like to see an in vivo gene mutation followup,
11 not just a micronucleus test or (indiscernible) test
12 and then I don't know about the determining whether I
13 should healthy subjects. Depending on the answers to
14 the first two.

15 DR. MIRIAM POIRIER: I just have a
16 question. Do they always analyze the generic? In
17 other words, can you assume that chemically you're
18 talking about two products that are exactly the same?
19 So, somebody comes along with a generic, you already
20 have a brand drug on the market. Do you
21 (indiscernible) analyze the generic that you're given
22 so you know it's the same or not?

1 DR. BOB BRASH: So by regulation, the
2 generic must have the same API as the (indiscernible)
3 listed drug, must be the same exact chemically.

4 DR. MIRIAM POIRIER: (indiscernible).

5 DR. BOB BRASH: The same identity. The
6 same (indiscernible).

7 DR. MIRIAM POIRIER: Okay.

8 DR. BOB BRASH: I wanted to ask a
9 followup question to doctor -- so a positive Ames
10 assay would an appropriate followup be the potent
11 carcinogenicity study?

12 DR. ALAN BOOBIS: No, because there are
13 other effects that can be a consequence of mutation --
14 gene mutation. So that would be part of the weight of
15 evidence, but I think you'd also want to satisfy
16 yourself that it's not in vivo (indiscernible) as
17 well. Because mutagenicity is an end point and so is
18 in vivo.

19 DR. BOB BRASH: Okay. In vitro
20 mutagenicity is the first signal?

21 DR. ALAN BOOBIS: Yeah.

22 DR. BOB BRASH: Second step, in vivo

1 mutagenicity?

2 DR. ALAN BOOBIS: Yes. And if you've
3 got the cancer (indiscernible) assay, that would be
4 very useful confirmatory (indiscernible).

5 DR. BOB BRASH: (Indiscernible).

6 DR. ALAN BOOBIS: Yeah.

7 WOMAN 3: I already have -- right, Bob?
8 We already have the answer -- the results of the
9 cancer, of the (indiscernible), right?

10 DR. BOB BRASH: Yes.

11 WOMAN 3: Yeah.

12 MAN 5: If it's chronically
13 administered.

14 DR. BOB BRASH: If it's chronically
15 administered.

16 MAN 5: I mean, there are two things
17 here. One is that technology moves on and we have
18 tests today, like the transgenic rodent assay that we
19 didn't have five or 10 years ago, and so depending on
20 when the innovator drug was approved, you may have
21 less information now than you would, had it been
22 approved more recently.

1 So that's part of the weight of
2 evidence that Alan is talking about. But one of the
3 things I'm wondering about is at some point, somebody
4 at CDER made a decision that here's a mutagenic API
5 and we are going to allow it in patients, so they have
6 been through a process of thinking through exactly
7 what is the risk.

8 We think it's okay. Why is that not --
9 why can't you use that thought process to say, here is
10 the risk for one to 14 doses to a healthy volunteer,
11 it does or does not meet our standard for safety for a
12 healthy volunteer?

13 What's changed since you approved the
14 NDA for (indiscernible)?

15 DR. TIMOTHY MCGOVERN: Well, I think
16 part of it is, the drug is approved for a disease
17 indication and so depending on the severity of that
18 indication, so it may be fine for 14 days, may be fine
19 for chronic use in that particular indication, but I
20 would argue it's a different scenario -- if you're
21 going back to healthy volunteers for a bioequivalent
22 study, that's a different risk/benefit assessment.

1 And then, just going back to that issue
2 of what's -- the scenario if you have a positive
3 mutagen but you have your standard to your
4 carcinogenicity assays could include a transgenic
5 assay as well that was negative.

6 From the CDER standpoint, we -- I think
7 we would generally say that's sufficient for
8 addressing potential carcinogenicity, but if that were
9 -- we're using the gene tox battery for, I know EPA,
10 other organizations, also use it for heritable changes
11 as well, so, but we do have the reproductive tox
12 battery as well. So I think from -- if I had the
13 positive mutagen and somehow it got all the way to
14 approval and that positive -- carcinogenicity studies
15 were well conducted and negative, that would be my key
16 piece of information I'd be looking at.

17 DR. TIMOTHY ROBISON: We had a
18 (indiscernible) where it was a positive Ames
19 metabolite. We allowed the drug to go forward in
20 patients for a short period of time, 28 days. And
21 this is several years ago. Prior to exceeding 28
22 days, they had to have a six-month (indiscernible)

1 carcinogenicity studies.

2 DR. AISAR ATRAKCHI: But not -- you
3 didn't' allow it in healthy people.

4 DR. TIMOTHY ROBISON: No.
5 (indiscernible) where there was a (indiscernible). I
6 mean, today, it might look more towards an in vivo
7 (indiscernible).

8 MAN 6: The policy or practice of
9 allowing some of those studies in healthy volunteers
10 is not really based on any risk/benefit data, that --
11 this is about 10 to 12 years ago, where
12 (indiscernible) policy assessment and that it was just
13 the belief that, well, there's a threshold of single
14 doses, not likely to do harm, and that we needed to
15 not -- to aid drug development.

16 So it was more of a practical
17 determination rather than any risk/benefit
18 determination.

19 MAN 7: Thanks for that, John, because
20 this confuses me a little bit and Dan's point, weight
21 of evidence has already been done with the reference
22 listed drug, whether it's a (indiscernible) we

1 administered or even if you don't have
2 (indiscernible). It was approved with the innovator
3 with a weight of evidence conclusion of what
4 carcinogenic risk already is. So now you're talking
5 about a generic that comes along.

6 You should be able to take that weight
7 of evidence -- you should know enough about the
8 innovator to say, is one dose or two dose or three
9 doses cancerous. The data should already be there. I
10 certainly wouldn't advocate doing additional or new
11 studies to try to determine, well, was that old weight
12 of evidence wrong?

13 Is it actually a carcinogen? Because
14 now, you're screwing around with the innovator, too.
15 (indiscernible) something.

16 MAN 6: Can I clarify this?

17 MAN 7: Yeah, sure, because I'm a
18 little confused by this.

19 MAN 6: The studies done in healthy
20 volunteers with the innovator may not have been done
21 in the United States, and so we may not have weighed
22 in on the risk/benefit determination. Now, the

1 generic comes in and wants to do a study in the United
2 States that changes the paradigm.

3 MAN 8: You do also have the
4 opportunity to do some post-market surveillance and
5 ask if there's any data on cancer in patients who have
6 been taking the drug, which is something that you
7 could never for (indiscernible) entity.

8 DR. AISAR ATRAKCHI: We can. We have
9 to have a good reason to ask for it. [OVERLAPPING
10 SPEAKERS].

11 MAN 9: We're also trying to protect
12 your patients, because you have -- you now have a drug
13 of higher risk that you know you cannot address in the
14 normal drug development process, but you have data in
15 the patients in the United States who've been taking
16 the approved drug and you can ask, is --

17 DR. AISAR ATRAKCHI: (indiscernible).

18 MAN 9: You can ask. I mean, this is
19 the hot topic de jour of Health Canada and a lot of
20 the genetic toxicologists is whether mutagenicity is
21 in and of itself a risk factor and so that's part of
22 the current scientific debate, if you will, of our

1 time and so now, when you get a generic drug which is
2 Ames mutagenic, you can answer that question because
3 you have access to the data.

4 DR. BOB BRASH: Just to circle back on
5 kind of (indiscernible) question about that weight of
6 evidence and going back and reevaluating the -- I
7 really wouldn't go back to reevaluate mutagenicity or
8 carcinogenicity (indiscernible) for sure. That's left
9 to the NDA. We would go on the given information in
10 the RLD label. We would go further in characterizing
11 the safety of the impurities in the generic
12 formulation.

13 For example, if they were not present
14 in the RLD, so it's those things outside of the RLD
15 that we might characterize the safety of to make sure
16 that they're in bounds, but we wouldn't further the
17 API safety (indiscernible).

18 MAN 10: I just wanted to add --

19 DR. AISAR ATRAKCHI: Identify yourself.
20 Name.

21 MAN 10: Oh, sorry. (indiscernible).
22 I'm (indiscernible). I just wanted to add that the

1 bioequivalent studies done (indiscernible) are to
2 advise the viability of generic drugs for the API and
3 the reason is that (indiscernible) changed so the
4 (indiscernible) of drugs may change (indiscernible) the
5 toxicity of API. They're looking at the bioequivalent
6 (indiscernible) difference in the (indiscernible)
7 drugs.

8 DR. AISAR ATRAKCHI: So for Part A,
9 which test results should receive the greatest
10 consideration and the weight of evidence? So would we
11 follow up with another mutation test or would we
12 follow up with (indiscernible).

13 DR. ALAN BOOBIS: I mean, I'm assuming
14 you have the data.

15 DR. AISAR ATRAKCHI: That's true. We
16 do.

17 DR. ALAN BOOBIS: Yes.

18 DR. AISAR ATRAKCHI: So --

19 DR. ALAN BOOBIS: So you're looking to
20 see if there was an appropriate followup of any
21 positive.

22 DR. AISAR ATRAKCHI: Correct.

1 DR. ALAN BOOBIS: Because I assume
2 what's why the question was asked in the first place.

3 DR. AISAR ATRAKCHI: Right.

4 DR. ALAN BOOBIS: So there's a positive
5 somewhere in vitro. You'd want to see what was the
6 followup on that, which would contribute to your
7 conclusion. I mean, as I've said, if you've got a
8 bioassay, which you should have on the innovative
9 drug, then that would also be substantial evidence it
10 was a clean bioassay and a clean followup, then you
11 see, well, I don't see there's any real concern of a
12 Phase 1 study or bioequivalent study in healthy
13 volunteers.

14 MAN 11: (indiscernible), CDER.
15 Actually, I saw one consult to the (indiscernible) for
16 generic drug, so the results are (indiscernible)
17 toxicity is a little bit (indiscernible) and then a
18 followup study, like, (indiscernible), that was
19 clearly positive (indiscernible). And then the
20 (indiscernible) toxicity study was in that case,
21 however, the two-year (indiscernible) study is clearly
22 (indiscernible) complications.

1 So the label is more or less misleading
2 folks, (indiscernible), because the label claims that
3 based on (indiscernible) evidence, it's not a
4 mutagenic. So (indiscernible) little hard for the
5 generic drug. It's hard, like API (indiscernible), do
6 you consider safe (indiscernible).

7 DR. BOB DORSUM: So you recalled a very
8 interesting case. Typically, with generics, in order
9 to inform how generic applicants should develop their
10 drug, OGD, the Office of Generic Drugs, will post a
11 product-specific guidance out there that's available
12 for all applicants to see and it will inform how to do
13 the trial, and is that trial that I mentioned on the
14 slide (indiscernible) include healthy subjects,
15 include patients only.

16 So in order to come to that
17 determination currently, what the reviewers will do is
18 go back and take a look at what is the overall profile
19 of safety from that reference listed drug
20 (indiscernible). So that may be, in a sense, looking
21 for whatever signals may exist, it is certainly not
22 solely limited to gene toxic carcinogenicity

1 information.

2 I'm actually posing some of these
3 questions here today so that we can increasingly use
4 triggers from that drug label to initiate
5 (indiscernible) so that we can use the weight of
6 evidence more appropriately. So currently, we're kind
7 of trying to mirror what was done before, and that may
8 be sufficient in many cases.

9 But in cases where we have more
10 information that we could use better, that's what
11 we're trying to do and aiming to do, and so that's
12 where the questions are coming from and so I don't
13 know exactly how that product-specific guidance was
14 for that product, but my guess is that it was
15 evaluated according to the prior development program
16 and looked at by the clinical discipline to make that
17 assessment, according to the various present safety
18 signals for the product.

19 DR. AISAR ATRAKCHI: So do -- since
20 you're up there, Bob, do you think we have enough
21 comments to answer this question?

22 DR. BOB DORSUM: Yes. I think that 3B,

1 the question of are there any other factors relating
2 to generic toxicology, in intentionally left that open
3 as a question because, of course, we have to answer
4 these questions -- these sorts of questions, do some
5 thinking on it frequently.

6 So I had thought maybe weight of
7 evidence would be appropriate. I thought maybe the
8 rodent bioassay might be reasonable to use. But I
9 really wanted to also leave it open for our expert
10 panel to say, you know what, yeah, there's rodent
11 bioassay but what you should really be attempting to
12 do is this other thing.

13 So I'd like to leave it open. Is there
14 anything that we should consider as a trigger for,
15 let's look at this further, that we haven't already
16 talked about here today?

17 DR. TIMOTHY MCGOVERN: The only thing
18 that comes to mind for me is if, say, you had an Ames
19 positive that was also positive in carcinogenicity
20 assay and the sponsor, as part of the overall package,
21 went forward and conducting various studies to show
22 that that positive finding and carcinogenicity study

1 is not related to the mutagenic positive.

2 So that could possibly build an
3 argument to say, you have a threshold -- say, might be
4 more based on pharmacology, so you may have a
5 threshold effect in place that could potentially allow
6 dosing in healthy volunteers just because that
7 positive carci finding wasn't tied in with the
8 positive gene tox.

9 DR. BOB DORSUM: Thank you. So that
10 gets more towards, consider your margins, consider the
11 mechanism, science-based decision making if it is a
12 positive, is it relevant.

13 DR. TIMOTHY MCGOVERN: Right. And it
14 could be a question of how -- the label may just say,
15 positive gene tox, positive carcinogenicity. May not
16 have any of that underlying information that actually
17 supported approval.

18 DR. BOB DORSUM: That's right.

19 DR. TIMOTHY MCGOVERN: Yeah.

20 DR. BOB DORSUM: But fortunately, there
21 are some cases and labels that clearly state where,
22 perhaps, there is a signal of what are those margins

1 and sometimes the labels are (indiscernible)
2 descriptive in ways that are very informative, so --

3 DR. TIMOTHY MCGOVERN: Yeah.

4 DR. AISAR ATRAKCHI: But if you do have
5 -- if you do know from the label of the individual
6 drug that it is -- caused mutagenicity and it was
7 positive in carci study, would you still be
8 comfortable using healthy volunteers or at that point
9 you will not to the bioequivalent study in healthy
10 patients -- healthy subjects but you will go to
11 patients?

12 DR. BOB DORSUM: Positive
13 carcinogenicity --

14 DR. AISAR ATRAKCHI: Yeah, positive
15 carcinogenicity and positive -- right. Well, Ames or
16 the (indiscernible) or if they did the two-year
17 bioassay on the rat and they did the transgenics in
18 mice, it's positive.

19 DR. BOB DORSUM: Well, then data are
20 mounting towards, we need to be very cautious with
21 this and we would have to look at the mechanism
22 (indiscernible).

1 DR. AISAR ATRAKCHI: So you
2 (indiscernible) give it to healthy subjects
3 (indiscernible)?

4 DR. BOB DORSUM: That's not what I
5 said.

6 DR. AISAR ATRAKCHI: You said you would
7 look at other things, right? But --

8 DR. BOB DORSUM: Well, safety is a very
9 -- it's across all end points. It is not just
10 (indiscernible).

11 DR. AISAR ATRAKCHI: Correct.

12 DR. BOB DORSUM: So that's what I mean
13 by that. But that's mounting evidence towards,
14 there's risk there for healthy subjects, that that
15 would be --

16 DR. AISAR ATRAKCHI: So you'd still
17 consider doing the healthy volunteers, all this
18 mounting positive gene tox and carci?

19 MAN 12: Can you (indiscernible) as
20 well?

21 DR. AISAR ATRAKCHI: So I was
22 wondering, now you have all the data you wanted to

1 decide. Are you going to say no to healthy volunteer
2 study at this point because the gene tox data and
3 positive carci study, or you still look at other data,
4 other mechanistic study or dose ranges or any other
5 evidence to show it's not -- it's no harm to healthy
6 volunteers? I didn't get your response yet.

7 DR. BOB DORSUM: Okay. I think I'm
8 just being too indirect.

9 DR. AISAR ATRAKCHI: Because, I mean, I
10 think we're (indiscernible) answer the other question,
11 so you do have -- this is for generic, so the drug's
12 already approved. It's in the label. That says this
13 drug is mutagenic and carcinogen. Right? And now, it
14 comes to generics and you want to do the bioequivalent
15 study in healthy subjects.

16 You have that information. Would you -
17 - because here it's asking, are there any other
18 factors relating to genetic tox that should be
19 considered when determining if the study can go in
20 healthy subjects. So if you know those two end
21 points, mutagenic and carcinogenic, would you still --
22 what else would you want to have --

1 DR. BOB DORSUM: I don't think that you
2 can really ask for more information. I think
3 (indiscernible) or you can try to (indiscernible), but
4 it is data that are concerning at that point. I'd be
5 interested if the panel would suggest that there are
6 other information that we should be more thoughtful
7 about, so those data in and of itself, do raise
8 (indiscernible).

9 DR. ERROL ZEIGER: Well, presumably, if
10 you're talking about later date, you hopefully -- you
11 may have a lot more information about the clinical
12 effects of that particular substance or that class of
13 substances. You may also have, as was mentioned, more
14 information about the mechanisms of carcinogenicity
15 and how irrelevant that mechanism may be for humans as
16 opposed to compared to rats or hamsters.

17 So, which means, you might have to go
18 back and reassess the initial chemical, but it gives
19 you some guidance as to what data gaps you may have
20 for the equivalent and are there any areas of
21 knowledge that are now relevant to your question that
22 may not have been relevant 10 years ago when it was

1 first approved.

2 DR. AISAR ATRAKCHI: Yes, this was
3 exactly what I was going to say. I mean, the drug is
4 approved. It's been on the market for a while and now
5 it's coming as a generic, so -- and it's positive with
6 the Ames or any other genotoxic, it's positive with
7 the carci, so this must have been for a serious
8 indication. So probably it was given to healthy
9 volunteers when they started with the actual drug, so
10 I would go to the original NDA and see what happened,
11 did they give it to healthy volunteers, how many
12 doses, and just go from there.

13 WOMAN 4: But healthy volunteer study
14 may have been conducted without the (indiscernible)
15 point.

16 DR. AISAR ATRAKCHI: Yes.

17 WOMAN 4: So now, you have a different
18 stage to decide.

19 DR. AISAR ATRAKCHI: Yeah, we do have
20 the carci data but it's probably for a serious
21 indication. If it wasn't for a very serious
22 indication, I don't think we would see it, right?

1 DR. BOB DORSUM: My FDA label
2 (indiscernible), but there's some pretty interesting
3 profiles for gene tox and carci out there.

4 Do the search, and these are things
5 that are sometimes either available over the counter,
6 there are things that are commonly used mainstream,
7 and there are these results that are either positive
8 or negative in one study or another and I just want to
9 make sure that we're asking the experts the right way
10 to navigate those because sometimes a positive is
11 popping a way that's seemingly problematic when we do
12 have 10, 20 years of apparent mainstream usage
13 (indiscernible).

14 What about the signals (indiscernible)?

15 DR. ALAN BOOBIS: Can I just ask for
16 clarification? When you say there's some positives,
17 do those positives always include an Ames test? Are
18 you talking about somewhere in the in vitro gene tox
19 battery there's a positive which could be
20 carcinogenicity or aneugenicity but not gene mutation
21 as well? I mean, alternatively.

22 DR. BOB DORSUM: Right. There are some

1 that are positive Ames and then end up being negative
2 in carcinogenicity, for example.

3 DR. ALAN BOOBIS: But are there some
4 that are negative in Ames but positive in other in
5 vitro gene tox --

6 DR. BOB DORSUM: Yes.

7 DR. ALAN BOOBIS: Because the reason
8 I'm asking that is that I don't think that all in
9 vitro gene toxicity is equal. I think the
10 interpretation of a positive Ames is a little bit
11 different from the interpretation of a positive
12 aneugenicity assay or even a (indiscernible) exchange
13 assay.

14 DR. AISAR ATRAKCHI: Yeah, we're going
15 to get -- that's question four.

16 DR. BOB DORSUM: I'm looking forward to
17 that answer. Thank you.

18 DR. ROBERT HEFLICH: So presumably when
19 the reference compound was approved, you didn't do the
20 transgenic gene mutation assay and that would be a new
21 piece of information that might inform the decision
22 over and above the cancer (indiscernible).

1 DR. ERROL ZEIGER: Yeah, what I was
2 going to say is the various in vitro tests are not
3 complimentary. If something is positive in Ames and
4 it's not a carcinogen, it's more likely to be positive
5 in the other in vitro tests as well because we're not
6 measuring carcinogenicity in these tests. We're
7 measuring DNA reactivity or chromosome reactivity.

8 So the fact that it's positive in Ames
9 and also positive in in vitro micronucleus or mouse
10 lymphoma? doesn't add anything to the weight of
11 evidence that, wow, it's positive in three tests as
12 opposed to one; therefore, it's more likely. It
13 doesn't work that way. And for a number of the in
14 vivo tests, they're not -- and I don't know the data -
15 - the current data for the transgenic or the PIG-A,
16 but as a rule, they were not as sensitive as the in
17 vivo -- as the in vitro.

18 There are quite a few mutagenic in
19 vitro carcinogens that are negative in the bone marrow
20 assay, for example, and bone marrow micronucleus
21 assay.

22 So a positive in the in vivo assay may

1 add some feel-good assurance to the positive in vitro,
2 but a negative in vitro -- in vivo assay doesn't
3 detract from the predictivity of that positive Ames
4 test and there are a number of publications on this
5 from the NTP database and from larger databases that
6 show the in vivo bone marrow assay is not that
7 sensitive and not -- it doesn't correct the negative
8 Ames assay all the time.

9 I'm using the word "correct" as
10 providing the right concern.

11 DR. ROBERT HEFLICH: I think the lack
12 of sensitivity, though, (indiscernible) based on
13 target exposure. I mean, as far as any end point
14 (indiscernible) into that, but you're only measuring
15 bone marrow.

16 DR. ERROL ZEIGER: Yeah, exactly.

17 DR. ROBERT HEFLICH: If it doesn't get
18 to the bone marrow, you're not going to see anything.

19 DR. ERROL ZEIGER: Exactly. But
20 another concern I have for in vitro assay is that
21 (indiscernible) by the NCTR data on acrylamide, is
22 where you've looked at a number of tissues for

1 mutation and looked at a number of tissues for cancer
2 and the mutation tissues to not -- tissues that show
3 mutation do not always show tumors and the tissues
4 that show tumors do not always show mutation.

5 So there is a disconnect there, some
6 sort of mechanistic disconnect that we don't
7 understand.

8 DR. ROBERT HEFLICH: Yes. Well, the
9 next step is to measure the mutations that are
10 actually relevant to the end point, which means
11 measuring cancer-driving mutations which I'm not
12 suggesting that you do, but I mean, the reason why you
13 get expanded call maybe a data or mutation or it may
14 be promotion of a particular preexisting clone, and
15 both would be relevant to carcinogenicity.

16 DR. ALAN BOOBIS: Could I just clarify?
17 As I understand it, genetic toxicology community do
18 not consider an in-needle bone marrow micronucleus
19 assay as an adequate followup of a positive Ames in
20 vitro. They are talking about different set of assays
21 and we have come across this and we're writing the
22 guidance on it now for WHO; we should make this very

1 clear.

2 DR. AISAR ATRAKCHI: Well,
3 (indiscernible) micronucleus as a followup to the
4 Ames.

5 DR. ALAN BOOBIS: Yes.

6 DR. AISAR ATRAKCHI: Yes. I mean, it's
7 a different end point.

8 DR. ALAN BOOBIS: It's a different end
9 point.

10 DR. AISAR ATRAKCHI: Right, it's a
11 different end point and you need to follow up, which,
12 we'll get to that question. You need to follow up at
13 the end point. If it's a mutagenicity in Ames, you
14 need to follow it up with a mutagenicity test.

15 MAN 13: I have a very simple question
16 to all the expert panelists regarding mutagenicity and
17 carcinogenicity. Do we have a list of the two-year
18 study tumor list from rat, from mice that we know this
19 to be positive, if they are relevant to human? Can
20 you tell us what they are?

21 DR. ERROL ZEIGER: Well, I'll ignore
22 that last half question, but through the NTP database,

1 going onto the NTP bioassay database, I think they can
2 -- you can break it out by tumor type because we've
3 done it -- we did it a few years ago for mesothelioma.
4 You could identify all the chemicals that produce
5 mesothelioma and then look in the database to see if
6 they were Ames positive or Ames negative.

7 This doesn't go to the relevance,
8 whether this particular tumor is relevant to humans,
9 that's another issue and that's going to be decided by
10 the people who know rodent tumorigenicity and know
11 human cancer because there are certain -- for example,
12 the Zymbal gland carcinoma, I think it's in rats, we
13 don't have a corresponding Zymbal gland. If
14 something's positive just in the Zymbal gland, it's
15 called a carcinogen.

16 So I don't know how to bridge that gap
17 at this point. You need to get the pathologists from
18 both disciplines talking to each other.

19 MAN 13: And I believe there's one
20 (indiscernible) cancer is not relevant to human.

21 DR. ERROL ZEIGER: Well, it depends on
22 -- I think it's a mouse or rat thyroid cancer,

1 depending on the particular cell type, that's
2 considered not relevant to humans. But then again,
3 there are good mutagens that only produce thyroid
4 cancers. Is that relevant for humans? Only produce
5 thyroid in rats or mice. Is that relevant to humans,
6 because they are genotoxic.

7 A lot of the thyroid carcinogens are
8 not genotoxic, so --

9 MAN 13: I assume somebody should have
10 complete list of those.

11 DR. ERROL ZEIGER: Those lists are
12 available from the NTP studies and you may be able --
13 even able to get them through the IR, if there are IR
14 compilations, that let you search across
15 (indiscernible).

16 MAN 13: Thank you.

17 DR. ALAN BOOBIS: Can I --

18 DR. AISAR ATRAKCHI: Yes.

19 DR. ALAN BOOBIS: I just wanted to say,
20 it's not as simple as a list of tumors, types. It's
21 also, has to include mode of action. It's quite clear
22 hepatocellular carcinoma can occur in humans from

1 certain chemicals that do it in rats. But it's also
2 true there are many chemicals that cause
3 hepatocellular carcinoma in rats by a mode of action
4 that's totally irrelevant to humans.

5 The same with kidney. (indiscernible)
6 rat's kidney is a mode of action that is irrelevant to
7 humans, but we can get real tumors by other mechanisms
8 or modes of action, so you have to look at tissue and
9 mode of action.

10 DR. ROBERT HEFLICH: I think the issue
11 of using rodent carcinogenicity data to make decisions
12 is somewhat problematic. I mean, but it's the best we
13 have.

14 Of course, we know there are
15 differences between rodents and humans as far as their
16 mechanisms of carcinogenesis and just to go back to
17 cancer driving mutations, I mean, there are different
18 sets of cancer driving mutations in rodent than human
19 -- tumorigenicity, finding those that overlap and
20 relate to one another is the trick for making the
21 rodent carcinogenicity assay truly predictive of human
22 cancer.

1 I think that's where there's
2 (indiscernible).

3 MAN 13: I just wanted to follow up
4 (indiscernible) for you, sir. I assume when we make a
5 decision, whether that's relevant or not, depends on
6 the mechanism of action, correct?

7 DR. AISAR ATRAKCHI: Yes.

8 MAN 13: But we might not know, are
9 there mechanism of action that we don't know. Isn't
10 that true?

11 DR. ALAN BOOBIS: Yes, and you're not
12 going to assume, therefore, on the side of caution
13 that if we don't know that it's potentially relevant.
14 That's just the way risk assessment works.

15 DR. AISAR ATRAKCHI: So if -- we should
16 move on to question four. Moving a little bit away
17 from mutagenicity and the question is, certain drugs
18 may be clastogenic but not mutagenic. Should
19 consideration be given to the mechanism of action and
20 genotoxicity, in designing studies is healthy
21 subjects?

22 We have talked about this but I think

1 the questions is here, so I'd like to hear from the
2 panel.

3 DR. ERROL ZEIGER: The nice thing about
4 clastogenicity is that it's something you could easily
5 monitor in human subjects as opposed to gene mutation
6 which is not as easy to monitor.

7 DR. AISAR ATRAKCHI: What do you mean,
8 you can do it in humans?

9 DR. ERROL ZEIGER: Well, you draw the
10 blood from somebody and you essentially can look for
11 chromosome damage in the white blood cells or --

12 DR. AISAR ATRAKCHI: We have tried to
13 do this over the years, but it's not a very --
14 sponsors don't like to do that, for liability issues
15 because, especially in healthy -- well, it's actually
16 neither one, healthy or patients -- if their test
17 becomes positive, the result is positive for
18 chromosomal aberration, what's the obligation of the
19 sponsor to inform or not to inform that patient or
20 that subject?

21 So it is difficult to do. Otherwise,
22 even lymph (indiscernible) test can be done and -- but

1 it's not done. I think that's a little bit --
2 ideally, yes.

3 DR. ERROL ZEIGER: Well, there is
4 enough data to show that an increase in the peripheral
5 blood micronucleus or chromosome aberration is
6 associated with increased cancer risk. So to answer
7 this question, I don't see, if you have a scientific -
8 - forget about the legal, the other thing -- if you
9 have a scientific way of simply answering the
10 question, is there an increase in chromosome damage in
11 patients, then that essentially addresses your
12 question here.

13 DR. AISAR ATRAKCHI: Sure.

14 DR. ROBERT HEFLICH: You can measure --
15 excuse me -- PIG-A and HBRT in humans --

16 DR. AISAR ATRAKCHI: Right.

17 DR. ROBERT HEFLICH: -- correctly,
18 although the end point is not validated the way --
19 same way the micronucleus and the chromosome
20 aberrations were, respect to the kind of study. I
21 mean, that was an incredible undertaking to do that.

22 DR. KEVIN PROHASKA: I'd like to add to

1 that last point that was made. I'm looking to go
2 about being able to monitor for something. It's not
3 my area of expertise, but if there's a reasonable way,
4 a reliable way of monitoring for an adverse event, it
5 ought to be included in the safety mitigation plan for
6 the study.

7 And with regards to the liability that
8 sponsors may have for finding these problems, it's
9 hard to have much sympathy on that, I'm afraid. You
10 guys, there is not only just a legal liability to
11 identify these problems but a moral liability. They
12 really are (indiscernible) they've identified some
13 serious adverse event they should be aware of.

14 DR. ROBERT HEFLICH: Well, that's
15 always been the pushback, the liability problem.

16 DR. AISAR ATRAKCHI: I mean, I just --

17 DR. ROBERT HEFLICH: -- industry is
18 (indiscernible).

19 DR. AISAR ATRAKCHI: I guess one way
20 around that is probably to collect -- especially in
21 healthy subjects -- you can collect the blood from any
22 -- X number of subject, therefore, you're not going to

1 really know -- as long as they're healthy, you're not
2 going to know the blood belongs to who and you can do
3 the study that way.

4 DR. ROBERT HEFLICH: There should be a
5 way of knowing whose blood is whose, you know, I would
6 hope. Yeah, so (indiscernible) conversation.

7 DANIEL LEVY: A followup comment for --
8 question for -- (indiscernible) from Biogen.
9 (indiscernible) going back to in vitro testing with
10 (indiscernible) NIEHS.

11 So your comment about monitoring
12 patients for, say, increasing their chromosomal breaks
13 and lymphocytes or micronucleus in the blood, but
14 isn't that a population-based analysis in that you
15 can't be precise for each individual whether their
16 increase in micronuclei will be a liability. Is that
17 correct?

18 DR. KEVIN PROHASKA: Well, it's not my
19 area of expertise, of course, but that's why I added
20 the caveat, if it's reliable and actionable
21 (indiscernible). So if there's some reason to believe
22 that the information is not reliable, then there could

1 be an argument for not informing people, but if it's
2 reliable, people ought to be informed.

3 DR. ERROL ZEIGER: Actually, everything
4 we've been talking -- all the numbers we've been
5 throwing around about genotoxicity and its predictive
6 value, that's in a way, all population based. It's
7 all retrospective study. The fact that 75 percent of
8 the salmonella positives are rodent carcinogens
9 doesn't tell you what that -- what this chemical today
10 that's positive, whether or not it'll be a rodent
11 carcinogen. Leave it at that.

12 DAN LEVY: You can -- this is Dan Levy
13 again. You can design a study where you take samples
14 before and after administration of the drug and see if
15 there's an increase in micronuclei and I think most of
16 us would think that's a pretty reliable way, if it's
17 positive, of saying there's a pretty high risk of
18 clastogenic damage in that individual.

19 I will remind you that the micronucleus
20 assay, while it, in terms of correlation of rodent
21 micronucleus results and rodent cancer results it's
22 extremely specific but very insensitive. That is,

1 many compounds including Ames positive compounds that
2 are carcinogens, are negative in the rodent
3 micronucleus assay.

4 In human micronucleus assay, there are
5 a lot of studies in the literature of biomonitoring of
6 people who are exposed to a variety of known
7 clastogens and known carcinogens and, for example,
8 cigarette smoke is known to have a variety of both
9 mutagenic and clastogenic compounds in it, but most
10 micronucleus studies of cigarette smokers do not find
11 an increase in peripheral blood micronuclei.

12 It's simply not sensitive enough to
13 detect it in people who are exposed to what we know is
14 an environmental carcinogen -- an environmental
15 genotoxic carcinogen. So getting a positive result in
16 a patient or a healthy volunteer in the micronucleus
17 assay, I think, would be a very strong indicator of
18 risk and I think very actionable and I -- considering
19 relative noninvasiveness and inexpensiveness of that
20 test, I don't understand why you wouldn't be doing it.

21 But a negative is not as definitive as
22 a positive result, which is fine. I mean, in some

1 ways, you want to get the most potent things. You
2 want to remove the most potent risks, and if you had a
3 relatively simple and reliable test to get rid of some
4 of them, you can consider using it.

5 DR. ALAN BOOBIS: I think this is -- I
6 have some thoughts on it, but I think this doesn't
7 really get to the answer to question four. But before
8 I do try and answer question four, I agree what Dan
9 said, but the fact is, I suspect -- I know of no study
10 of that type. Do you? Do you know of that --

11 DAN LEVY: I'll send you a list.

12 DR. ALAN BOOBIS: Sorry?

13 DAN LEVY: I'll send you --

14 DR. ALAN BOOBIS: In which they gave --
15 they did the study in a group of healthy volunteers
16 before and after --

17 DAN LEVY: Oh, no, no, no.

18 DR. ALAN BOOBIS: No, I know
19 (indiscernible) studies in populations as far as --
20 but I suspect the reason they'd be doing C-positives
21 is because pretty well nobody is going to get a drug
22 which is going to cause a positive micronucleus test

1 in a patient -- in a volunteer. That would have to be
2 a pretty good genotoxic, and to do that.

3 DR. ROBERT HEFLICH: It was done with
4 AZT.

5 DR. ALAN BOOBIS: Sorry?

6 DR. ROBERT HEFLICH: It was done with
7 AZT.

8 DR. ALAN BOOBIS: Yeah, but that's a
9 particular compound, particular class -- group of
10 patients. I mean, the sorts of drugs we're talking
11 about here today, which is the present forms of that.
12 But that's -- I mean, this is (indiscernible). I
13 think the answer to question four is, very much so.

14 I would want to know about the
15 mechanism of action, so how does that compound cause a
16 non-gene mutation, genotoxic effect because we know of
17 many modes of action or mechanisms which are
18 thresholded and would not translate into a significant
19 risk at the sorts of exposures we're talking about in
20 these clinical trials.

21 There are others that would, but there
22 are many that would not. So that information would

1 really help moving forward.

2 DR. AISAR ATRAKCHI: Thank you. I just
3 want to say, AZT pretty much does it always.

4 DR. ALAN BOOBIS: Yeah.

5 DR. AISAR ATRAKCHI: It's a
6 transplacental carcinogen. It's also a clastogen.
7 It's also a mutagen. So it doesn't... Okay.

8 DR. ROBERT HEFLICH: So just to follow
9 up on Dan's, the problem with cigarette smoke is that
10 it's an inhalation exposure which is very inefficient
11 in exposing the bone marrow. That's the basic
12 problem, why cigarette smoke is negative in most bone
13 marrow type assays.

14 DR. AISAR ATRAKCHI: Yes. I do have a
15 question from people online. I was going to go
16 through the questions and then ask or, should I do it
17 now? I could. You want me to do it now? Okay, so
18 one of the -- the first question, I'm just going to
19 read them. For Kevin, Dr. Prohaska's presentation,
20 what is told by FDA currently to patients in the
21 informed consent or exposure to an Ames positive drug?
22 I don't know what that --

1 DR. KEVIN PROHASKA: I'm sorry, I don't
2 know if I follow the question. They asking whether or
3 not we have any policy as to what --

4 DR. AISAR ATRAKCHI: I think so, yes.

5 DR. KEVIN PROHASKA: Okay. None that
6 I'm specifically aware of; however, if there are
7 preclinical concerns, my thought is they should be
8 discussed or described in the consent document.

9 DR. AISAR ATRAKCHI: Okay. Would this
10 drug be suitable for a healthy volunteer study? The
11 parent was negative in Ames without S9, but there are
12 human-specific metabolites that are Ames positive in
13 TA100. Is there an allowable threshold for the level
14 of these metabolites, 1 percent, 10 percent versus 50
15 percent of total exposure?

16 DR. TIMOTHY MCGOVERN: Sounds like a
17 case-by-case type evaluation.

18 But getting back to that initial
19 question, I mean, what I typically would see for any
20 kind of positive gene tox result, it would be in the
21 informed consent stating what the response is, our
22 concern being that there's an association with that

1 positive response to induction of cancer and some type
2 of -- it's always difficult words, especially -- I
3 haven't seen one for a positive Ames assay, but some
4 statement regarding risk -- potential risk to the
5 subject.

6 So there definitely would be something
7 in the informed consent.

8 DR. AISAR ATRAKCHI: Okay. The next
9 question is from -- this is for (indiscernible)
10 presentation. From what was presented so far, it is
11 still not clear to me what Ames positive IND does mean
12 here. Ames positive is the only information we have
13 as gene tox information. The drug is Ames positive
14 but negative for clastogenicity in vitro and/or in
15 vivo.

16 The drug is positive in Ames and both
17 in vitro and in vivo for clastogenicity or the drug is
18 Ames positive and considered clearly mutagenic in vivo
19 in humans. The different scenarios imply different
20 potential risk for the patients as potential of in
21 vivo relevance may be different.

22 Does the single dose causing cancer

1 correlate with the 25,500-fold compound-specific TTF -
2 - which is the TD50 over 50,000 -- for those compounds
3 with lifetime carci studies available?

4 DR. BOB DORSUM: I think the first part
5 --

6 DR. AISAR ATRAKCHI: Can you use the
7 mic?

8 DR. BOB DORSUM: I think the first part
9 there, inquiring what type of data are available and
10 what's the relevance of that, so as we discussed
11 earlier, the only data that are available at the point
12 of Phase 1 clinical trials are the Ames data. For the
13 second part of the question, I'm not sure I have the
14 expertise to answer that.

15 DR. AISAR ATRAKCHI: What is TTF?
16 Maybe it's TTC? It's a typo? So the question is,
17 does the single dose causing cancer correlate with the
18 TD50 divided by 50,000 for those -- I guess that's the
19 acceptable intake -- for those compounds with lifetime
20 carci studies available.

21 DR. BOB DORSUM: I don't know that
22 those comparisons were ever made for any of the

1 studies we looked at.

2 DR. AISAR ATRAKCHI: Okay. So this
3 next question --

4 DR. TIMOTHY MCGOVERN: I'll take a
5 stab. So you have, yes, TTC is based on lifetime
6 carcinogenicity studies. I don't think it
7 incorporates any of the single dose-type studies
8 (indiscernible). So it probably does not -- I mean,
9 it may call into the point that TTC of 1.5 micrograms
10 per day is still protective in considering the results
11 of the single-dose studies, but it wasn't used to
12 develop that curve, if you will.

13 DR. AISAR ATRAKCHI: The next question
14 is, are there certain Ames assay strains that are
15 particularly predictive or suggestive of positive
16 carci studies.

17 DR. ERROL ZEIGER: No.

18 DR. AISAR ATRAKCHI: Some better than
19 others?

20 DR. ERROL ZEIGER: No. They're
21 measuring different target sites, so the fact that
22 something hits a 5C sequence or 5G sequence, this one

1 hits a 6G sequence doesn't tell you anything about a
2 relative potency or relevant predictability.

3 DR. AISAR ATRAKCHI: Is exposure to a
4 metal really the best approach when considering
5 duration? Maybe that was beryllium question. Is
6 exposure to a metal really the best approach when
7 considering duration? I'm not sure why not. Okay.
8 Currently ICH S1 only requires carcinogenicity testing
9 for drugs used for a total of six months or more. Do
10 these data suggest that all drugs should be tested
11 regardless of their duration of use?

12 DR. ALAN BOOBIS: I mean, I don't think
13 it does. I think we're talking about the value of
14 genotoxicity testing data and (indiscernible) what
15 more information you would be asking for, I think that
16 if you have good negatives in genotoxicity, good
17 repeat dose toxicity, you can certainly get to a
18 situation where you wouldn't be asking for a
19 carcinogenicity study for all drugs, as we do now.

20 DR. AISAR ATRAKCHI: Tim?

21 DR. TIMOTHY ROBISON: I just want to
22 come back the Ames positive metabolite that -- in a

1 lot of situations, we (indiscernible) the same as the
2 API, sort of pursued them, and I think there was one
3 case example where it was extremely low and we sort of
4 went through an argument where maybe nothing was made
5 of it. For the most part, we treated them equivalent
6 to the API and it needed to be pursued in terms of
7 testing.

8 DR. AISAR ATRAKCHI: But presumably
9 that metabolite is, like present -- it's a major
10 metabolite.

11 DR. TIMOTHY ROBISON: Well, I mean,
12 yeah. I mean, generally, but we didn't use the 10
13 percent threshold for an Ames positive metabolite. We
14 pursued them in terms of further testing.

15 DR. AISAR ATRAKCHI: Then moving on to
16 question five relating to ICH S2R1 guidance provides
17 recommendation for followup for a positive in vitro
18 (indiscernible) clastogenicity assay. If a drug is a
19 mutagenic, Ames positive, are there followup studies
20 to assess risk that should be conducted prior to
21 conducting studies in healthy volunteers?

22 If so, would a 28-day transgenic rodent

1 mutation assay, which includes a PIG-A end point, be
2 appropriate or -- well, okay, and if it was positive,
3 then you stop there. If it was negative, the tissue
4 evaluation should proceed.

5 Alternatively, instead of the 28-day
6 transgenic, would a 26-week (indiscernible) mouse
7 carci study or (indiscernible) bioassay be requested?

8 So now, we need to know if -- what
9 would be the followup test which we kind of talked
10 about a little bit earlier, about the followup for
11 positive Ames test.

12 PATRICIA ESCOBAR: Patricia Escobar
13 from Merck. I just have a clarifying question in your
14 (indiscernible) you're assuming that we do have
15 (indiscernible) mutation assay and to that, we
16 advocate the PIG-A end point. Actually, there are two
17 different assays. You can do a transgenic 28-day
18 study and you can do a PIG-A Assay, so they're
19 different -- two different (indiscernible) so I just
20 want to clarify (indiscernible).

21 DR. AISAR ATRAKCHI: Yeah, I think the
22 point is the followup with in vivo mutation.

1 PATRICIA ESCOBAR: But it could be
2 either.

3 DR. AISAR ATRAKCHI: It could be
4 either.

5 DR. MIRIAM POIRIER: -- build the end
6 point into the transgenic mutation assay.

7 DR. AISAR ATRAKCHI: Oh, yeah, yeah.
8 That's right.

9 DR. MIRIAM POIRIER: (indiscernible)
10 end point into the assay.

11 DR. ROBERT HEFLICH: the idea was to
12 make it easier. If you got a positive PIG-A, the
13 transgenic becomes not important.

14 PATRICIA ESCOBAR: Yeah, but, for
15 example, they said we're going to use it. You can do
16 a 28-day study as your first -- (indiscernible) 28-day
17 study and you have an inform -- a PIG-A end point.

18 DR. ROBERT HEFLICH: Right, but by --

19 PATRICIA ESCOBAR: -- positive, you
20 stop it, right?

21 DR. ROBERT HEFLICH: Yeah.

22 PATRICIA ESCOBAR: Like, you're not

1 going to do a 28 (indiscernible) study.

2 DR. ROBERT HEFLICH: The problem is if
3 the PIG-A is negative, then can't really rule out a
4 tissue-specific response you could pick up with the
5 transgenic.

6 PATRICIA ESCOBAR: But I thought that
7 (indiscernible) between the PIG-A assay was actually
8 to be another -- a surrogate in vivo mutation assay
9 comparable to the 28 transgenic.

10 DR. ROBERT HEFLICH: I'd like to think
11 that, but I mean, that's not an accepted...

12 PATRICIA ESCOBAR: Because I
13 (indiscernible). As far as I understood, the
14 (indiscernible) that's how we've been kind of thinking
15 about it. We have not used it a lot. There's a lot
16 of information out there, just not as much, but that's
17 the idea, to do one or the other, both of them in vivo
18 mutation end points, which is the way --

19 DR. ROBERT HEFLICH: The way we
20 recommend doing it is combined assay at this point
21 because of the uncertainty about the PIG-A.

22 DR. AISAR ATRAKCHI: Thank you.

1 MAN 14: So I have a question about the
2 28-day transgenic. Even the most mutagenic
3 carcinogens generally only cause tumors in three,
4 maybe four tissues in a rodent study.

5 Bob mentioned earlier about the
6 acrylamide study where the mutations and the tumors
7 weren't in the same tissues or there was some overlap
8 but not total overlap, and so the question is, how do
9 you decide how -- in which and how many tissues you
10 need to sample in the transgenic assay before you've
11 got enough data to make a decision and how can you say
12 that that's equivalent to a single PIG-A end point?

13 So we know -- we really know very
14 little about the relative sensitivity of various
15 tissues in the transgenic mutation assay. There's
16 very, very little data on that. I spent two years,
17 three years on a HESI committee looking over a lot of
18 those data and it's very sparse. And so it's not
19 clear to me how you come to a conclusion that you have
20 enough data to understand which tissues and how many
21 tissues to sample. And so I would be curious how you
22 plan to develop that recommendation.

1 DR. ROBERT HEFLICH: I think in TG488,
2 there's recommendations as to how we choose tissues,
3 based on what you know about the distribution of the
4 chemical and its metabolism. Just follow that --
5 those guidelines, as far as setting up a transgenic
6 assay.

7 The data in the transgenic gene
8 mutation database has been collected over 30 years and
9 some of it's pretty bad. I mean, it was generated
10 using antiquated methods, so I think if you look at it
11 in total, we can say, this is junk, you know.

12 But if you -- I think, I'd like to
13 believe, if you conduct a transgenic assay following
14 the current guidelines, that you'll get a reasonable
15 estimate of mutation in particular tissue. It's clear
16 that there's a lot more data in some tissues than
17 others, but anyway, in theory you can look at
18 anything.

19 DR. AISAR ATRAKCHI: But I just wanted
20 to clarify, I think the point here from A is you're
21 doing the 28 transgenic rodent mutation test, but
22 incorporate into it the PIG-A. But you're saying

1 that's -- you're saying they're two different studies.
2 I don't think we will object to how it's incorporated
3 unless there's technical issues that --

4 PATRICIA ESCOBAR: No, no, you can
5 incorporate them if you want to, but we were seeing
6 those assays as separate assays, so you could choose
7 one or the other. So not necessarily that you needed
8 to do the two at a time. Here, you're suggesting to
9 do them at the same time.

10 Doing the assay at the same time is
11 feasible because at the end of the day for PIG-A, the
12 only thing you take is blood and then you just run the
13 PIG-A. So that's the easy part.

14 That's why we thought, if you do a 28-
15 day study, the (indiscernible) study or a 28-day
16 study, you could actually at the PIG-A end point and
17 get that important -- not necessarily going into this
18 28 transgenic --

19 DR. AISAR ATRAKCHI: So 28 days, non-
20 transgenic?

21 PATRICIA ESCOBAR: Yes, or 28 days non-
22 transgenic. Yes.

1 DR. ROBERT HEFLICH: If I can predict
2 how the guideline is shaping up, I would say that it's
3 possible to do just PIG-A if you can -- like the in
4 vivo micronucleus assay, if you can argue that you're
5 getting adequate exposure of the bone marrow to the
6 reactive metabolites, that may be by alteration in the
7 reticulocyte frequency or something like that.

8 But you'd be taking a risk of having
9 your data -- if you got a negative in PIG-A, the FDA
10 might come back to you and say, well, you should do
11 this (indiscernible) or something.

12 DR. ERROL ZEIGER: And as you know, if
13 you do it all in the transgenic, you can still look at
14 PIG-A, but freeze away other tissues and then you have
15 -- you might throw them out or you might need to
16 analyze them or want to analyze them.

17 DR. ROBERT HEFLICH: That was exactly
18 the argument.

19 PATRICIA ESCOBAR: No, that's a good
20 option. I'm just saying, the way we were interpreting
21 it the last couple of years was completely separate.
22 This is a different way of seeing it. I'm not saying

1 it's right or wrong.

2 DR. ROBERT HEFLICH: Well, we're
3 forward thinkers here at the FDA.

4 DR. AISAR ATRAKCHI: So just to wrap up
5 this question, is there a preference of using either
6 the 28-day transgenic or the 26-week Tg.rasH2 as a
7 followup?

8 DR. ERROL ZEIGER: I'm not sure what --
9 how much information is available on the effectiveness
10 of the Tg.rasH2. I know it was tested with a lot of
11 known carcinogens, a lot of alkylating agents, but as
12 far as other chemical classes, I have no idea of that.
13 I don't know if the data exist or if somebody just
14 hasn't pulled them together yet.

15 DR. AISAR ATRAKCHI: So you're saying
16 the 28 -- you'd go the 28 day?

17 DR. ERROL ZEIGER: I don't know enough
18 about the Tg.rasH2 to say yes.

19 DR. AISAR ATRAKCHI: Okay.

20 DR. ROBERT HEFLICH: I think without
21 knowing very much about it either, I think there is a
22 history of positives in it that may not be

1 informative.

2 DR. ERROL ZEIGER: Looks like --

3 DR. ROBERT HEFLICH: To put it
4 elegantly.

5 DR. ERROL ZEIGER: It's like the early
6 TGR transgenic studies. People only tested chemicals
7 they expected to be positive. I don't think anybody
8 put a Ames negative -- more than one or two Ames
9 negative chemicals into a TGR study in the early days,
10 because they were looking for positives. They were
11 trying to develop the system and see how well it
12 works.

13 And from the little I know about the
14 Tg.rasH2, we might be in the same situation. We know
15 these are carcinogens. Let's see how this responds to
16 it, which doesn't really tell you anything.

17 The example was, a number of years ago
18 somebody came into a lab saying, I have this wonderful
19 bacterial test that identifies all carcinogens. And
20 he showed that the dozen or two dozen alkylating
21 agents were positive and carcinogens. And one of us
22 asked the question -- I don't remember who -- well,

1 how does this test do with non-carcinogens? And the
2 answer was, well, we're not interested in finding non-
3 carcinogens.

4 So yes, if you're going to only test
5 chemicals you think will be positive, the test will
6 look good.

7 DR. ALAN BOOBIS: The other point about
8 the transgenic mutation assay is it's available in
9 both rat and mouse; whereas, the Tg.rasH2 is only
10 available in a mouse. That could be significant.
11 It's a lot quicker to get turnaround on results and I
12 think there's a lot more data now in positives and
13 negatives. And there's fewer false positives in the
14 transgenic mutation assay. The Tg.rasH2 assay
15 responds to not only genotoxic carcinogens.

16 PATRICIA ESCOBAR: I wanted to clarify
17 this and actually, and actually some other information
18 out there, I don't know the literatures, but
19 (indiscernible) part of (indiscernible). They're
20 accepting the Tg.rasH2 to cover a full set of
21 chemicals, genotoxic and non-genotoxic
22 (indiscernible). So it is a known and well accepted

1 assay.

2 DR. TIMOTHY MCGOVERN: I was going to
3 add that maybe more of a practical stepwise approach,
4 if you have a positive Ames assay, you might want to
5 start with a 28-day study just to get their clinical
6 program up and rolling again eventually, assuming it
7 is a long-term administration drug, you'll need your
8 two rodent model carcinogenicity which could include
9 the 26-week Tg.rasH2.

10 But you could, probably, if you wanted
11 to bypass the 28-day study, you could go straight to
12 the 26-week Tg.rasH2 as well.

13 DR. BOB BRASH: Well, one thing about -
14 - Dan probably would like to comment on this is
15 there's an interest in substituting the in vivo common
16 assay for a gene mutation end point and there's data
17 in the literature that just came out this year,
18 arguing that this is inadequate substitute. I wonder
19 how other -- whether you'd accept common assay data in
20 lieu of gene mutation data for a decision like this.

21 DR. ALAN BOOBIS: It depends. I think
22 common assay has a lot of merit, but I think it also

1 has to be interpreted very carefully because we know
2 you can get high dose false positives from non-
3 genotoxic modes of action. If you -- because it's not
4 measuring a direct gene mutation (indiscernible).

5 It's something consequence to that and
6 that's a valid end point, but I think as long as it's
7 interpreted properly and the study was designed
8 correctly, then yes, it can (indiscernible). I think
9 in the absence of other in vivo follow-ups, it could
10 be (indiscernible).

11 DR. DOUGLAS BRASH: One thing to keep
12 in mind with the common is (indiscernible) assay is
13 very sensitive to the first couple of hits and then it
14 just plateaus and so if you're also looking at DNA
15 (indiscernible) for example, you're going to see a
16 dosage bounce. It goes up, it's flat (indiscernible)
17 higher doses.

18 Now if you wait for repair, you're
19 going to think, (indiscernible) there's nothing,
20 nothing, nothing, nothing's happening, then boom, the
21 last couple of things (indiscernible) you see it. So
22 you do have to be very careful.

1 DR. AISAR ATRAKCHI: We have three or
2 so questions from online. With respect to ICH M7
3 referred to earlier were 120 micrograms for 30 days
4 would be acceptable for an impurity with clear Ames
5 positive data and not belonging to a class of well-
6 known, highly potent mutagenic carcinogens, how likely
7 would you assume such an Ames positive compound to
8 represent a new class or highly potential mutagenic
9 carcinogen?

10 DR. TIMOTHY MCGOVERN: It's a tough --
11 how likely? Repeat that last part.

12 DR. AISAR ATRAKCHI: Okay, not
13 belonging to a class of well-known, highly potent
14 mutagenic carcinogens, how likely would you assume
15 such an Ames positive compound to represent a new
16 class or highly potential mutagenic carcinogen?

17 DR. TIMOTHY MCGOVERN: I say we
18 generally would assume it not likely to represent a
19 high potency.

20 DR. AISAR ATRAKCHI: Yes, I think so.
21 If a drug is shown to have an equivocal Ames result,
22 what followup studies would constitute an acceptable

1 rate of evidence argument as shown to be negative?

2 For example, a panel member mentioned the in vivo PIG-
3 A, or would more need to be done?

4 WOMAN 6: (Indiscernible).

5 DR. ERROL ZEIGER: If it's equivocal,
6 you go back to basic scientific principles. You do a
7 repeat assay and you do it with maybe a little bit
8 more substance to it, more doses or additional
9 strains. But if it's equivocal, it calls out for
10 repeat tests because the difference between a negative
11 and equivocal and a positive could just be a few
12 mutants on a couple of plates.

13 MAN 15: Have you published a paper
14 recently on that?

15 DR. ERROL ZEIGER: So did you.

16 DR. ALAN BOOBIS: Can I just say that
17 this is a decision -- mission-critical decision. In
18 other words, the answer to the question is, do you
19 need a resolution of the answer or could you move
20 forward, assuming a positive? And maybe you can. If
21 you come up with a strategy that says there's a
22 certain amount you could give as a single dose or two

1 doses to your volunteers, then making that assumption
2 allows you to move forward, okay. If it's critical to
3 resolve the question, then yes, you'd follow the
4 strategy of repeat dose and then think of followups.
5 So I think it's not necessarily essential that you
6 resolve every question, if you can move forward
7 (indiscernible).

8 DR. ERROL ZEIGER: Well, based on some
9 studies that were done a number of years ago, these
10 weak positives are much less likely to repeat than a
11 clear -- something that's clearly negative. So I've
12 always been an advocate of repeating your results with
13 a positive or negative, doing a repeat test because
14 these weak positives, like I said, two people with
15 slightly different interpretations of the twofold
16 rule.

17 They have one coming up called negative
18 (indiscernible) equivocal or positive. It takes less
19 time and less effort to repeat it than to discuss it.

20 MAN 15: One of the things I want to
21 point out is there's a big difference between
22 repeating a two-year cancer bioassay and repeating an

1 Ames test. It is the cheapest, quickest test in our
2 armament and in a few weeks, you can get an answer and
3 if that settles your question, that's a lot easier
4 than a lot of other things you might want to work on.

5 WOMAN 7: Yeah, actually
6 (indiscernible) panel of experts, especially from FDA
7 so the (indiscernible) a question. For example,
8 (indiscernible) clinical (indiscernible) for first the
9 human side (indiscernible) for Phase 2 study, it can
10 be (indiscernible) and of course there are some
11 (indiscernible) for the formulation (indiscernible)
12 test, but for the solution for (indiscernible)
13 clinical test.

14 And also (indiscernible) to rely on a
15 possible Phase 2 we will rely on Phase 2
16 (indiscernible) and the (indiscernible) move forward,
17 the healthy volunteer study (indiscernible) or we need
18 to provide all this (indiscernible) more relevant
19 Phase 2 study. It's a (indiscernible).

20 DR. TIMOTHY MCGOVERN: I think you'd
21 want to submit all the data. And I would be looking
22 for rationale as to why you're getting different

1 results in your two assays because sometimes you could
2 be purifying material, the original result could've
3 been due to potent impurity that was present and no
4 longer there, but I think it would probably raise some
5 eyebrows initially.

6 They had one positive, one negative,
7 and we'd be looking for some investigation as to why
8 you saw a difference in that result and why we should
9 rely on the negative one as opposed to the positive
10 one.

11 WOMAN 7: Yeah, that's a very good
12 comment. We all think about that, actually.
13 (indiscernible) in different labs, but all
14 (indiscernible) and (indiscernible) from one country
15 to another, so the labs (indiscernible) different
16 vision, too, and of course the Phase 2 one is more
17 mature clinical (indiscernible) potential.

18 DR. AISAR ATRAKCHI: I mean, that's
19 like Tim was saying. You need to -- once we see
20 differences in results, clearly it's better -- we will
21 ask the questions. So instead of us asking you the
22 question, just provide the explanation why you think

1 there was a difference in (indiscernible) as opposed
2 to the back and forth.

3 WOMAN 7: Okay, thank you. So
4 basically the whole information need to provided and a
5 real story line thing, you guys will judge on that.

6 DR. AISAR ATRAKCHI: Another question
7 is, it was mentioned that the PKC for mutagenic
8 impurities was 3.8 milligram for one day for ICH M7.
9 If so, then what is the justification for giving one
10 to four doses of an Ames positive compound to healthy
11 volunteers that is likely a much higher dose than for
12 the impurity?

13 DR. DOUGLAS BRASH: That's why we're
14 here today.

15 DR. AISAR ATRAKCHI: Correct. Okay.
16 Coming back to the main topic, how would the panel
17 rate negative results from a combined comet
18 micronucleus study? I assume it means, if you have
19 results from comet micronucleus test and they are
20 negative, how would --

21 DR. ERROL ZEIGER: If the Ames test was
22 positive, I would --

1 DR. AISAR ATRAKCHI: And those are
2 negative. I think that's what --

3 DR. ERROL ZEIGER: And those are
4 negative, they -- going along with what was said, I
5 would not denigrate or I would not reduce the impact
6 of the Ames positive.

7 DR. AISAR ATRAKCHI: Right.

8 DR. ERROL ZEIGER: The fact that it's -
9 - and we did a study of this for -- in was a couple of
10 (indiscernible) committee that was formed five years
11 ago to look at this. What does it take to cancel out
12 the implications of the Ames positive? And it clearly
13 came out at -- two papers were published. David
14 Kirkland is the first author on it. If the Ames test
15 is positive or negative in any of the in vivo studies,
16 did not -- an eliminate the probability that it would
17 be a carcinogen, but did not affect the probability it
18 would be a carcinogen.

19 DR. AISAR ATRAKCHI: It's different end
20 points. The assay (indiscernible).

21 DR. ERROL ZEIGER: Different end
22 points.

1 DR. ALAN BOOBIS: That may be the
2 conclusion in that paper, but there are other groups
3 who's come to different conclusions, who's concluded
4 that if you've got good negative data on a measure of
5 the same end point, so comet assay and/or transgenesis
6 in vivo, then it might -- and with no evidence of
7 precursor effects in repeat dose study up to 90 days
8 or six months, it's enough to discount the positive in
9 vitro.

10 DR. ERROL ZEIGER: Sounds as if we need
11 a new group to get together and pull together all
12 these data.

13 DR. AISAR ATRAKCHI: But I think you're
14 saying is the overall weight of evidence.

15 DR. ALAN BOOBIS: Absolutely.

16 DR. AISAR ATRAKCHI: Yes. I don't
17 think you're saying the results of the Ames, ignore
18 it.

19 DR. ALAN BOOBIS: No.

20 DR. AISAR ATRAKCHI: Right. It's a
21 weight of evidence.

22 MAN 16: (indiscernible). All of us

1 know that the Ames positive mean something. We need
2 to deal with that. But I don't know if we remember
3 that as about -- over 20 percent of Ames test positive
4 will be negative in carci studies, so do we over-
5 emphasize the positive if there's other in vitro study
6 or in vivo study (indiscernible) study is negative and
7 we say decrease a little bit (indiscernible) Ames
8 test?

9 DR. AISAR ATRAKCHI: The 80 percent
10 prediction of the Ames test, it's -- when it's
11 positive, that's giving you its predicted -- these
12 compounds going to be likely they will be carcinogens.
13 So you will be -- they are two positive
14 (indiscernible).

15 You're missing the point percent and
16 it's a decision that we have all made that we are okay
17 with (indiscernible) missing 20 percent of the data as
18 a false negative. Or rather, false positive,
19 actually. False positive.

20 DR. ERROL ZEIGER: Part of that,
21 there's a fallacy in looking at sensitivity and
22 specificity, because a lot of these studies were done

1 with 50 percent to 90 percent carcinogens in the
2 population. So when you've got -- and the population
3 that you're looking at is -- Ames positives are much
4 less or the -- much less than that, carcinogens
5 (indiscernible) be much less than that.

6 If you look at -- there are some
7 publications that Ames test is 90-some-odd percent of
8 the publications where the Ames test is 10 to 20
9 percent. The more carcinogens you'll have in your
10 population of chemicals, the better your sensitivity
11 will be. Ideally, you have 100 chemicals and all of
12 them are carcinogens, you check every one, you've got
13 sensitivity of 100.

14 Ten percent of non-carcinogens, you
15 check off every one, you've got a sensitivity of 90.
16 It still looks good. But if only 10 percent of them
17 are carcinogens, you check off every one, your
18 sensitivity is only 10 percent.

19 This is something that was pointed out
20 by Cooper in one of his originally two-by-two table
21 presentations, that the proportion of true positives
22 in the population that you're looking at will look at

1 how effective the test looks.

2 MAN 16: Yeah, another problem with
3 these correlations is that we really do not have a
4 very accurate list of genotoxic carcinogens and non-
5 genotoxic carcinogens and genotoxic non-carcinogens,
6 so for example, estrogen is definitely a carcinogen.
7 There are actually some studies that show it's
8 genotoxic.

9 But nobody thinks that it's a
10 carcinogen because of its genotoxicity. The mechanism
11 is well known that its qualities as a hormone binding
12 to a receptor are what makes it carcinogenic.

13 DEHP, non-genotoxic carcinogen. We
14 know a lot about how it causes liver cancer. It has
15 nothing to do with genotoxicity. If you were to do a
16 two-by-two table it would seem, oh, the Ames test
17 misses DEHP because it doesn't detect it as a
18 carcinogen. Well, of course it doesn't. We don't
19 want it to detect it as a carcinogen.

20 And a lot of the lists that you see of
21 genotoxic carcinogens and non-genotoxic carcinogens
22 are merely based upon Ames results without knowing,

1 without mechanism of action when it's known, and there
2 are a fair number -- unfortunately, many of the
3 compounds for which the mode of action, mechanism of
4 action is really, really well understood, the data
5 comes from studies that are not in open literature but
6 they're in the files of CDER, the Office of Pesticide
7 Programs, and so forth where they -- not a lot of
8 these kinds of studies and as far as I know, nobody's
9 really assembled that very high-quality data into an
10 overall study and so you have to understand the
11 correlations in those two-by-two tables are just a
12 rough estimate and you cannot live and die by them.

13 MAN 17: Another problem is, there was
14 no clear, agreed-upon definition of what is a
15 genotoxic. There are dozens of tests that measure
16 mutation, recombination, strand breakage. Where do
17 you stop? Where do you stop? Right now, the current
18 is, if it's positive in one of the ICH assays it's
19 considered genotoxic.

20 MAN 16: I mean, glyphosate is
21 genotoxic because it causes (indiscernible) exchanges.

22 MAN 17: Yeah. (indiscernible) nobody

1 does anymore, because it was very (indiscernible) is
2 very sensitive to the particular protocol you're
3 using. That's why nobody does it, but yes. There's
4 no definition. John Ashby used to use, if it's
5 positive in salmonella, it's a genotoxin. But then,
6 he would define genotoxin by positive in salmonella,
7 positive in salmonella --

8 DR. TIMOTHY MCGOVERN: Circular.

9 MAN 17: But this is part of the
10 problem and there are a number of chemicals that we
11 know are genotoxic that cause rodent tumors but do not
12 cause rodent tumors based on their genotoxicity.

13 One example that I was involved with
14 that came to FDA is something that was weakly
15 mutagenic in the Ames test, which doesn't mean that
16 much, but it produced tumors only in the presence of
17 chronic inflammation and chronic necrosis, and only in
18 the animals where you had the chronic inflammation and
19 chronic necrosis.

20 Now, is that -- is it a genotoxic
21 chemical? Is it a genotoxic carcinogen? Or is it
22 some other mechanism? We don't have the science at

1 this point and I don't think we have the discipline at
2 this point to say, yes, it's genotoxic but no it is
3 not a genotoxic carcinogen.

4 DR. ALAN BOOBIS: Well just to -- for
5 information, the chemical (indiscernible) which is the
6 European counterpart of (indiscernible), I think it
7 is, long range initiative, has funded the construction
8 of a database along exactly the lines you're
9 suggesting where they're try -- I mean, it is a
10 judgment call, but they have people like David
11 Kirkland involved, to try to determine which of the
12 carcinogens are carcinogenic by a genotoxic mode of
13 action and by non-genotoxic mode of action and which
14 chemicals have they got which are negative.

15 And they're going to release a curated
16 database of several hundred chemicals later -- early
17 next year, probably, that -- and the idea was, the
18 start of this was to try to underpin the TDC for
19 genotoxic carcinogens more substantially with a
20 curated database, but grounded to try to provide the
21 sort of information we're asking for now. Which of
22 the carcinogens are carcinogenic by genotoxic mode of

1 action and which are not?

2 So hopefully we'll get a quantify of
3 data (indiscernible).

4 MAN 17: I thought ECVAM had already
5 done that.

6 DR. ALAN BOOBIS: Excuse me?

7 MAN 17: I thought ECVAM had already
8 done that.

9 DR. ALAN BOOBIS: They did, putting
10 together a list of genotoxicants but not -- they
11 haven't curated the CPDB database.

12 MAN 17: (indiscernible).

13 DR. ALAN BOOBIS: Well, David
14 Kirkland's involved in both.

15 MAN 17: Okay, yeah, I know it was the
16 first offer from the ECVAM study. One thing I've
17 learned from doing two-by-two tables for the PIG-A
18 gene mutation validation exercise with David Kirkland
19 is that the outlier, the non-concordant chemicals in
20 explaining why they're non-concordant, is often the
21 most valuable part of the study because there are
22 always going to be things that are negative from what

1 your prediction you would like to have because of a
2 reason.

3 And the reason is very informative as
4 to the nature of the assay.

5 DR. AISAR ATRAKCHI: So I'd like to
6 move on because the last question I'd like the panel
7 to address -- and I think question six, perhaps, can
8 move on quickly because we've discussed a lot of the
9 points here.

10 Can you provide guidance for a path
11 forward for development of a DNA reactive drug, for
12 example, the need for a mechanism of action,
13 structural considerations, functional groups at the
14 molecular level, (indiscernible) cross comparisons
15 (indiscernible) molecules with a known safety
16 information, observed genotoxic response, mutagenic,
17 clastogenic, aneugenic, or followup assays that
18 described in the earlier question, which is the
19 alternative (indiscernible) test or the two-year
20 bioassay?

21 Is there anything else we can add to
22 this information? I think there is an agreement that

1 we would like -- it's helpful to know the mechanism of
2 action. It's helpful if we know there is a structural
3 alert that can add to the weight of evidence. Whether
4 -- is it more important to know if it's mutagenic or
5 clastogenic or aneugenic?

6 But if we have this information, I
7 think we can add that to the weight of evidence and I
8 think we just discussed the followup assays. Is there
9 anything else that we can add to this?

10 DR. ALAN BOOBIS: I think C, read
11 across from (indiscernible) can be extremely powerful.
12 If you know what -- you've got a very good idea what
13 the chemical reactivity of the new entity that's
14 driving the positive and you've got an existing
15 compound with the same reactivity and a similar
16 profile in vitro, but you've got a vast amount of
17 human experience because it's been used for years as a
18 human medicine. Then, you can use that information
19 for read-across very effectively.

20 MAN 17: I think you're saying here if
21 you have an Ames positive (indiscernible), we say
22 stop, not going to allow this to be given in humans

1 because there is a risk, although we can't clarify it
2 very well, you're going to have to give us more
3 information.

4 DR. ALAN BOOBIS: This is sort of
5 (indiscernible).

6 MAN 17: And that's what we're -- yeah.

7 DR. ALAN BOOBIS: Yeah.

8 DR. AISAR ATRAKCHI: Okay. And the --
9 oh, and I guess Part F is to allow microdosing of such
10 drug without any followup assessment. I think we've
11 addressed that as well earlier.

12 The last question, are there drug
13 classes or specific drugs targeted to the
14 (indiscernible) that should never be administered to
15 healthy subject? Think we had some slides to show on
16 this. Okay, there we go. So this is an introduction
17 to the epigenome consist of specific (indiscernible)
18 modifications of chromative components which include
19 DNA, RNA, and proteins that (indiscernible)
20 inheritance of differentiating states.

21 Structure and function of the epigenome
22 are controlled by these covalent marks which are

1 applied by enzymes which are the riders to the
2 (indiscernible) 47 base pair of DNA and the eight
3 (indiscernible) components of a nuclear cells. These
4 marks instruct and the proteins that recognize them,
5 the readers, to identify and remodel particular
6 genomic regions to modulate gene expression,
7 plasticity of the epigenome (indiscernible) much to
8 the existence of erasers that is the enzymes capable
9 of (indiscernible) active and repressing marks.

10 Tumor cells not only are activated by
11 genetic, epigenetic alterations, but also
12 (indiscernible) epigenetic processes to ensure their
13 escape from chemotherapy and host immune surveillance.
14 And there has been a growing emphasis of recent drug
15 discovery efforts on targeting the epigenome that
16 includes (indiscernible) modification. Several new
17 drugs are being tested and some are already approved
18 by the FDA.

19 Neoplastic, for example, lymphoma and
20 pre-neoplastic lesions have been observed in
21 toxicology studies with (indiscernible) as short as
22 three months in duration which is highly unusual. Is

1 it appropriate to use healthy subjects for these types
2 of (indiscernible)?

3 DR. ALAN BOOBIS: There are a number of
4 drugs which we've been giving to healthy volunteers
5 and patients for a long, long time which affect the
6 epigenome, so valproic acid is one of them. It's a
7 (indiscernible) modulator. And we have never been
8 concerned about the risk of giving a few doses to
9 volunteers of these drugs.

10 The question is, are we going to
11 reappraise our entire approach to giving any drug to
12 ensure that it doesn't affect epigenome before we give
13 it to a patient, because it may -- or a volunteer,
14 because it may not be designed to hit as an anti-
15 cancer drug. It might just be an incidental effect.
16 And we have the clinical experience of some of these
17 compounds already.

18 DR. ROBERT HEFLICH: Isn't it somewhat
19 outside the scope of this workshop.

20 DR. AISAR ATRAKCHI: It is.

21 DR. ROBERT HEFLICH: I mean, because
22 these things are likely to be Ames positive.

1 DR. AISAR ATRAKCHI: Yeah. It was a
2 question that --

3 DR. ROBERT HEFLICH: Unless you
4 (indiscernible).

5 DR. AISAR ATRAKCHI: -- wanted an
6 answer to.

7 WOMAN 8: There's been no correlation
8 between results of gene tox and findings of
9 carcinogenicity in animals or in humans, so that's why
10 the question is out there. We don't know which ones
11 are carcinogenic and after how many doses.

12 So while we're seeing an animal
13 carcinogenicity, we hear carcinogenicity in animals
14 with several of these drugs, we don't know if that --
15 a single dose will be priming the gene such that
16 effects could be seen later on or this is after
17 chronic administration or multiple dose administration
18 that these effects would be seen in animals. So
19 again, it's been seen in animals, medications.

20 DR. BOB BRASH: What's the indication?
21 Are these anti-cancer drugs?

22 WOMAN 8: Yes, but animals are healthy.

1 Yes, so if we see carcinogenicity in the animals, but
2 patients -- you see it also in patients
3 (indiscernible) is not strong.

4 DR. AISAR ATRAKCHI: It is anti-cancer
5 drugs, yes?

6 WOMAN 8: Yeah.

7 DR. ALAN BOOBIS: Are these both types
8 or the methylase -- demethylase types? The
9 methylation demethylation or with the histo
10 modulations as well?

11 WOMAN 8: Well, I don't know how -- how
12 much information --

13 MAN 18: Methylating inhibitors, not
14 with the (indiscernible).

15 DR. ALAN BOOBIS: Okay, that makes
16 sense.

17 WOMAN 8: Yeah, not the -- yeah. Okay.

18 DR. ALAN BOOBIS: (indiscernible) that
19 we know, that don't --

20 DR. AISAR ATRAKCHI: Have you mentioned
21 the target? No.

22 MAN 18: We had experience with the

1 Ames positives. We have some basis of making a
2 decision, but we have -- with these drugs that
3 particularly target the epigenome and single dose, we
4 don't really know what a single dose might do multi
5 generation. So without that data gap, question is, is
6 that that under the current climate, should healthy
7 volunteer studies be excluded with drugs designed to
8 target the epigenome? (indiscernible).

9 DR. DOUGLAS BRASH: So I'm guessing
10 that this class of drugs is going to get bigger and
11 bigger over the next few years. And so the concern I
12 have about it for the fact (indiscernible) although
13 nobody talks about it, we (indiscernible) mutations.
14 Years later, you become mottled with tumors
15 (indiscernible) which by itself does nothing.

16 But if you have a mutation you now get
17 the tumor. These go back to experiments. You know,
18 the most famous (indiscernible), so forth. These go
19 back to the (indiscernible). So then if you have
20 these, this class of drugs, it becomes relevant --
21 maybe not whether this one is the Ames -- the positive
22 drug, but was there something else ever, or your

1 hamburger last week or whatnot, that then does show up
2 (indiscernible).

3 WOMAN 8: So some of these are negative
4 in all three battery of assay. A mechanistic study --

5 DR. DOUGLAS BRASH: Thank for reminding
6 me to say it. So in the '70s, there was a push to
7 have an assay system or (indiscernible) support
8 promoters and for various reasons it never took off.
9 But so the answer is, I don't think we have any
10 database to compare to as to when this would happen.

11 MAN 18: Yeah, I mean, remember, the
12 battery is based on specific mechanisms, none of which
13 apply to that particular class. I'll point out that
14 there are a lot of things that affect methylation --
15 folic acid, folate, vitamin D (indiscernible) -- so I
16 think the problem we have is that we don't have a
17 screening assay that can tell you whether your drug is
18 a potent enough inhibitor to create those tumors, and
19 so that's a huge hole and without any assay, the
20 answer is, we can't tell anybody what to do or not to
21 do because we don't have any rational way of
22 approaching it.

1 I mean, if we know that these drugs are
2 being developed specifically as anti-tumor agents,
3 what's the chance that somebody will accidentally
4 develop a similar compound for another indication
5 against which it appears to have efficacy and it turns
6 out it's doing the same thing that these drugs are
7 doing on -- the same effects on the epigenome, do we
8 have a mechanism that will find that out in our entire
9 armament of pre-clinical screens?

10 And that's the question I think we
11 really need to answer is, what do we need to start
12 looking at to pick up the most potent or at least --
13 either this mechanism or at least the most potent
14 versions of it? Now, if a 90-day study is all you
15 need because you're seeing tumors in a 90-day study,
16 then maybe that's your answer.

17 WOMAN 8: Well, we see pre-neoplastic
18 lesions in one-month studies with some of these drugs,
19 but -- so until such a day that we have the
20 mechanistic studies or something else, should we
21 exclude healthy volunteers?

22 MAN 18: I don't think anybody -- I

1 think that's an easy question to answer. I think, to
2 me, the real conundrum is whether there are other
3 drugs that are being developed like that that we
4 should start worrying about. That, to me, is the
5 bigger -- drugs and other products. That's the big
6 concern that -- you've uncovered the tip of the
7 iceberg of a new mechanism of toxicity for which we
8 may not have an adequate screen, for not only healthy
9 volunteers but also for patients.

10 DR. BOB BRASH: For sure, you should
11 exclude healthy smokers.

12 WOMAN 9: So if carcinogenesis is --
13 carcinogenesis is complex. So we're still talking
14 about DNA damage, but now we know there's
15 inflammation, so to me the tipping point is metastasis
16 and I remember reading one paper, there's a model and
17 this was in a mouse and metastasis was dependent on
18 epigenetic changes.

19 So I think we have to leave open the
20 concept that different interactions are -- may affect
21 different steps in carcinogenesis and maybe we need to
22 develop some tests to look to these mechanisms.

1 MAN 19: Talking about oncology, I
2 mean, I'm in the Division of Psychiatry. We have a
3 lot of neurodevelopmental diseases and now they're
4 supposed to start entertaining this kind of epigenetic
5 (indiscernible). They're trying to do something like
6 that.

7 Then, the other concern for
8 epigenetics, it could be transgenerational so you
9 might not pick up anything in the -- in your carci
10 study, but you can pick up in their offspring, but we
11 usually don't do that. I mean, we don't do carci
12 analysis in their offspring.

13 For repro studies it go up to data or
14 something like that or a little bit longer, but that's
15 not long enough to pick up any tumors, so I'm just
16 wondering what's the approach here or do the experts
17 have any recommendation for that?

18 DR. TIMOTHY MCGOVERN: Sounds like you
19 should reexamine the yellow mouse and model. Maybe
20 Trosko's metabolic cooperation test -- I mean, going
21 back a ways there, but, I mean, people have thought
22 about this in the past.

1 DR. ERROL ZEIGER: Also, if you're
2 thinking transgenerational, then you're thinking a lot
3 more than cancer reduction. You're thinking unknown
4 mental --

5 MAN 19: Right.

6 DR. ERROL ZEIGER: -- effects.

7 MAN 19: Right.

8 DR. ERROL ZEIGER: Which would be
9 easier to detect because they'd be detectable at the
10 young age of (indiscernible) and that could be
11 (indiscernible).

12 MAN 19: So for, like, specific to the
13 question, should the drug be administered to healthy
14 subjects, I mean, especially for neurodevelopmental
15 diseases and...

16 DR. ALAN BOOBIS: You could start by --
17 I don't know how ethically permissible it would be,
18 but you could probably make an argument that you avoid
19 women of childbearing age or potentially pregnant
20 women. That would overcome a transgenerational
21 impact.

22 MAN 19: That's true.

1 DR. ALAN BOOBIS: Most likely.

2 DR. AISAR ATRAKCHI: But so -- sorry,
3 you're done?

4 MAN 19: Yeah, I'm done.

5 DR. AISAR ATRAKCHI: So are there other
6 classes of drugs -- not necessarily just the epigenome
7 but anything else that you can -- that the panel can
8 think of that should not be administered to healthy
9 subjects?

10 DR. BOB BRASH: Well, you're talking
11 about a whole series of non-genotoxic carcinogens. I
12 think a lot of mechanisms --

13 DR. AISAR ATRAKCHI: Yeah, I mean --

14 DR. BOB BRASH: Several mechanisms.

15 DR. ALAN BOOBIS: You don't give them
16 to healthy volunteers (indiscernible).

17 DR. BOB BRASH: Well, then there might
18 be a different answer for each class.

19 DR. ERROL ZEIGER: Well, at this point,
20 where we are now we don't know they're non-genotoxic
21 carcinogens. We just know they're non-genotoxic.

22 DR. AISAR ATRAKCHI: Right.

1 DR. ERROL ZEIGER: But where do you go
2 from there? Well, one thing -- didn't mention that
3 relates to some of the other questions, one thing we
4 haven't discussed is look at the chemical class.
5 There are some chemical classes that seem to be the
6 predictivity of a positive (indiscernible)
7 carcinogenicity is 90 percent or more. There are
8 others, like single aromatic amines.

9 Half of the false positives in the NTP
10 database are these aromatic amines; although they're
11 very good mutagens and not coming up positive in the
12 animal. So looking at the chemical structure and the
13 relationship of that chemical structure to
14 carcinogenesis can give you a lot of interesting
15 information.

16 DR. AISAR ATRAKCHI: Okay, any other
17 questions? I only have one more question from online,
18 but I thought we had discussed this. If a compound
19 has (indiscernible) specific metabolite S9 related
20 which caused Ames positive but not in mice and human,
21 what is the suggested followup study?

22 DR. ALAN BOOBIS: What do you mean by

1 not in mice and human?

2 DR. AISAR ATRAKCHI: I guess it was not
3 positive.

4 MAN 20: (indiscernible) positive in
5 the Ames (indiscernible) S9 and it (indiscernible)
6 like other --

7 DR. AISAR ATRAKCHI: Oh, other S9.

8 MAN 20: (indiscernible) study and
9 (indiscernible).

10 DR. AISAR ATRAKCHI: Oh, it's a
11 (indiscernible) specific metabolite. I think if it
12 is, then I don't think we care. Right, I mean --
13 what?

14 DR. ALAN BOOBIS: Well, your weighted
15 evidence would argue --

16 DR. AISAR ATRAKCHI: Yes.

17 DR. ALAN BOOBIS: -- that there is not
18 a cause for concern.

19 DR. AISAR ATRAKCHI: Right. Exactly.
20 Okay, I think in absence of any more questions and
21 we're one minute away from 4:00, I really appreciate
22 all of you coming in and listening to this workshop as

1 well as a great and big thank you to all our panelists
2 and I think it was a very helpful workshop and
3 discussion and hopefully we can -- as an agency, we
4 can come up with some information that can advise us
5 and give us recommendations to move forward for --
6 have some plan in place to address these types of
7 compounds. Thank you so much.

8 (Whereupon, at 3:58 p.m., the
9 proceeding was concluded.)

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I, KEVON CONGO, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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