

1 Nitrosamines as Impurities in Drugs; Health Risk  
2 Assessment and Mitigation Workshop  
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7 Moderated by Anne Painter

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## A P P E A R A N C E S

## List of Attendees:

Anne Painter, Host

Dr. Aisar Atrakchi, Panelist

Dr. Gerhard Eisenbrand, Panelist

Dr. Soterios Kyrtopoulos Ph.D, Panelist

Dr. Joseph Guttenplan, Panelist

Dr. Mark Cronin, Panelist

Dr. Errol Zeiger, Panelist

Dr. John R. Bucher, Panelist

Dr. Jerry M. Rice, Panelist

Dr. Stephen S. Hecht, Panelist

Dr. Richard H. Adamson, Panelist

Dr. Michael DiNovi, Panelist

Dr. Sruthi King, Panelist

Dr. David Keire, Panelist

Dr. Deborah Johnson, Panelist

Dr. Timothy McGovern, Panelist

Dr. Robert T. Dorsam, Panelist

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## 1 P R O C E E D I N G S

2 MS. PAINTER: Hi, everybody. Thank you  
3 so much for joining day two of our workshop on  
4 nitrosamines as impurities in drugs. Before we get  
5 started, we just wanted to do another reminder of the  
6 house rules for today's workshop.

7 As a reminder, everybody who is not  
8 speaking, please keep your phone on mute. And all  
9 attendees will be muted, and only panelists will have  
10 the ability to unmute themselves.

11 If you are using the video feature,  
12 only the panelists that will be engaging in today's  
13 discussions will have their video feature turned on.  
14 If you are not speaking, please have your video  
15 feature turned off.

16 Regarding any questions and discussion,  
17 please submit any questions that you would like to  
18 have answered by using the Q and A feature to the  
19 bottom center of your screen in Zoom. Any questions  
20 that you do submit, we do have a team of moderators  
21 who are monitoring the Q and A chat box. If you see  
22 that your question has been dismissed, that means it



1 has been received by the team and sent to the  
2 moderators for review.

3 If you are a panelist who will be  
4 speaking, please utilize your chat feature, as the  
5 host will prompt you when it is time for you to  
6 present. When using the Q and A chat box, the  
7 moderators and the workshop host will work together to  
8 monitor the questions, and they will make sure that  
9 they are addressed as time allows during the workshop.

10 And additionally, today's meeting  
11 presentation and recording will be made available on  
12 the webpage later this week.

13 Thank you.

14 DR. ATRAKCHI: Good morning, good  
15 afternoon, and good evening, and welcome back to the  
16 second and last day of the workshop on nitrosamines as  
17 impurities in drugs. We had a productive and  
18 informative day yesterday and look forward to the  
19 discussions today. We continue with the remaining  
20 questions, starting with question five, the last one  
21 under Exposure and Risk Assessment.

22 Question five: Should the regulatory

1 limits for nitrosamines listed for food and water, or  
2 amount formed endogenously be considered in  
3 determining the acceptable intake of nitrosamines in  
4 drugs?

5                   Considering the abundance of  
6 nitrosamines, in and around us, should these amounts  
7 be taken into consideration to determine an acceptable  
8 intake in medicines. Keep in mind, one takes a drug  
9 as a patient to gain benefit to treat a disease or  
10 illness. It is not a choice that one makes. And the  
11 American public expects their medicines to be safe.

12                   However, as a personal choice, we eat  
13 how much we eat, and what we eat and drink -- is our  
14 own choice. Some authors -- and also, from  
15 yesterday's discussion -- stated that endogenous  
16 production of nitrosamines and their precursors are a  
17 more important source of exposure than exogenous  
18 intake.

19                   It is also important to keep in mind  
20 that in order to estimate the dietary intake, it is  
21 not only of nitrosamines, but in addition we need to  
22 estimate nitrates and nitrides, and not focus only on

1 diets that are rich in these compounds -- i.e., not a  
2 biased assessment.

3 So, with that, I would like to start  
4 with Dr. DiNovi.

5 DR. DINOVI: Yeah. Good morning. And  
6 thank you. So, this question has bothered me -- I  
7 guess is the right thing to say -- since we first  
8 started discussing it, because it is just -- there are  
9 lots of things, here, that are -- it is not obvious on  
10 the surface.

11 As an exposure assessor modeler --  
12 purely as a numerical person, I would say the answer  
13 is, no. Because the regulatory limits do not actually  
14 impact the inputs into my exposure assessment models.

15 But clearly, a bigger answer has to be,  
16 yes. And as we discussed extensively yesterday, as  
17 more and more information becomes available about the  
18 endogenously formed nitrosamines, that would certainly  
19 impact how you choose to pick an acceptable intake,  
20 which is, of course, a risk management mitigation  
21 metric.

22 The limits themselves -- it sounds

1 contradictory but setting a limit does not impact  
2 exposure very much. Unless you are in a position  
3 where many -- and I am thinking in terms of food,  
4 which is my world. Unless you are in a position where  
5 many of the products would become unacceptable at a  
6 level that you have chosen for safety -- so then, you  
7 are brining in all sorts of economic impacts -- which  
8 I do not think we are discussing, here -- the limits  
9 are typically set in a way that balances the ability  
10 to measure the numbers -- for example, at -- although,  
11 I do not think that is particularly a problem, here --  
12 with the cost, both in time and effort. We discussed  
13 this briefly yesterday, on getting here.

14           So that is why you can hear in my voice  
15 there is a hesitancy to just say -- you know, yes or  
16 no -- which is my normal choice for yes/no questions.  
17 But you clearly are going to have to take especially  
18 the endogenous formation into account when you get to  
19 the end, if the endogenous level is as we have heard  
20 three orders magnitude higher than the drugs, there  
21 would be no impact in picking an acceptable level from  
22 a numerical risk assessment point of view.

1                   As you said yesterday, Dr. Atrakchi,  
2     you do not want them in there at all. So, the CDER's  
3     goal is to get them out. And that is a separate  
4     question from my world modeling the risk. And I will  
5     be interested in hearing what my colleagues have to  
6     say. So, I will pass it along, now. Thank you.

7                   DR. ATRAKCHI: Thank you, Dr. DiNovi.

8                   Dr. Kyrtopoulos? You are on mute. We  
9     could move to Dr. Eisenbrand and go back to  
10    Dr. Kyrtopoulos in a moment.

11                  DR. EISENBRAND: Yeah. Thank you,  
12    Dr. Atrakchi. This is Gerhard Eisenbrand speaking.

13                  Well, I have made this -- I have  
14    commented on this point yesterday, already. And  
15    again, I would like to repeat that in my opinion, it  
16    would be a pragmatic way of using the dietary  
17    exposure, for instance, as a point of reference for  
18    the potential to validate or evaluate the potential  
19    risk coming from drug connected exposure.

20                  And while I, personally, would prefer  
21    to use, for the time being, the dietary exposure, is  
22    that it seems to me that although the data are, sort

1 of, 10 years old or some about that -- the database  
2 about the dietary exposure -- it still is valid, in a  
3 sense. And of course, one can confirm this -- I  
4 think, within a very reasonable timeframe, to be sure  
5 that the date had not moved very much, if at all. I  
6 would personally guess that they may, today, be even  
7 somewhat lower than before -- than 10 or 15 or 20  
8 years before.

9 But this is a relatively good database.  
10 We have a lot of data there. It is data dense, and it  
11 allows a -- what I would call a commonsense approach,  
12 saying -- well, we have this -- in my opinion, really  
13 more or less unavoidable exposure. I mean, you have,  
14 perhaps, a certain liberty -- degree of liberty to  
15 modify it by your personal preferences. But still --  
16 I mean, taking a reasonable medium amount of -- which  
17 we know is really below point five micrograms a day --  
18 it is around point two, depending on the country where  
19 it has been measured. So that is a database that is  
20 quite solid and could be used. I think the  
21 intravenous risk of formation is much more -- in my  
22 opinion, much more difficult to quantitate in terms

1 of -- you have a lot of, perhaps -- ability by the  
2 health status and nutritional status, and so on. So,  
3 my plea would be to not disregard this nutritional  
4 exposure as a potential point of reference to -- you  
5 know, evaluate the risk from -- in a -- one -- it is a  
6 common sense approach, in my opinion.

7 So, I think, that is what I want to  
8 say, here, to this point, again. Thank you.

9 DR. ATRAKCHI: Thank you,  
10 Dr. Eisenbrand.

11 Dr. Kyrtopoulos?

12 DR. KYRTOPOULOS: Can you hear me, now?

13 DR. ATRAKCHI: Yes. We can hear you.

14 DR. KYRTOPOULOS: Ah. Okay. I am  
15 please.

16 So, I have started saying, before, that  
17 I agreed with what Dr. DiNovi had said, to a large  
18 extent, in that we have this exposure from the diet.  
19 Possibly, we have a much larger exposure endogenously.  
20 We do have certain reservations, as we discussed  
21 yesterday. But it does seem that there is significant  
22 endogenous exposure. So -- and there are two ways in

1 which one can see this background -- let's call it --  
2 exposure in relation to the question we are  
3 discussing.

4 On one hand, one can say that there is  
5 this very large amount of exposure that is coming from  
6 sources other than the one we are interested in. And  
7 these sources -- the drug contaminants, are adding  
8 just a little bit to what is already a large number.  
9 So, there significance falls, in weight.

10 On the other hand, given that these  
11 background exposures -- especially the endogenous  
12 exposure -- if it worth -- for whatever value it may  
13 have, larger or smaller -- should be seen as  
14 contributing to the background incidents of cancer in  
15 the general population. I think that this was already  
16 stated, yesterday, by one of the panelists.

17 For example, taking the numbers that we  
18 are currently discussing -- assuming, for instance,  
19 that the mean -- average mean endogenous exposure  
20 holds true to the number of 144 micrograms per day  
21 that I mentioned yesterday -- that would seem, based  
22 on the Peto bioassay, to be -- to correspond to



1 something like a one percent lifetime exposure to  
2 that -- would be equivalent -- give rise to about one  
3 percent liver tumors. So that would be the  
4 contribution of dimethylnitrosamine to the background  
5 incidents of cancer. Which, overall, in humans, is,  
6 of course, much larger. It is in the order -- 30 to  
7 40 percent.

8 On the other hand, traditional risk  
9 assessment considers this acceptable exposures. Those  
10 exposures, which are predicted to result in an  
11 incremental lifetime risk of one in a 100,000. So,  
12 from that point of view -- it starts from the general  
13 incidents and counts what gives rise to an incremental  
14 risk. In other words, ignoring the -- this background  
15 incidents and the associated exposures.

16 I think that in principal, that would  
17 be the correct way to go about it. And this becomes  
18 even more valid if we assume that maybe we are over  
19 estimating endogenous exposure. If real endogenous  
20 exposure is not in the thousands of micrograms that we  
21 are currently suspecting, but it is lower, then it  
22 becomes -- the weight of the incremental exposure --

1 it becomes more significant, conceptually.

2 So, I think, that in principal, we  
3 should not be taking into account this background  
4 exposure, whether it is coming from endogenous  
5 sources, or from food, or whatever else.

6 On the other hand, having said that, I  
7 do recognize the need for an expediency for a  
8 practical approach, given everything that was said  
9 before -- that people have to take med -- these  
10 medicines. They have no choice. And it is a question  
11 of balancing risk and benefits.

12 So, I -- my overall final, kind of,  
13 position, would be that we should aim at estimating  
14 what is acceptable based on risks calculated without  
15 taking into account the background exposure. However,  
16 we need to be flexible in view of the particular  
17 expediencies which exist. That is it for me.

18 DR. ATRAKCHI: Thank you, very much.

19 Dr. Rice?

20 DR. RICE: Good morning. In listening  
21 to the views of the previous speakers, I have thought  
22 carefully about my own position on this question,

1 which some might consider simplistic. But I keep  
2 returning to the fact that the physiologic effect of  
3 environmental exposures to a given agent is a  
4 cumulative result of all systemic exposures to a agent  
5 that one may experience. And I think, in consequence,  
6 that one really must consider the amounts in food and  
7 water in the context of what one may decide is the  
8 acceptable intake of nitrosamines in drugs.

9           The balance of evidence seems to be  
10 that the amount consumed by drugs -- consumed in drugs  
11 is miniscule -- or, at least, very much smaller than  
12 what one experiences from intake in water -- and  
13 especially, in foods. And I think it would send a  
14 confusing message to consumers -- citizens in  
15 general -- to try to tell them that the body somehow  
16 knows whether a given molecule -- any given  
17 nitrosamine comes from a drug taken by necessity or in  
18 a food taken voluntarily. Once it enters in the body  
19 it is all the same irrespective of origin. And  
20 therefore -- very strongly believe that you must look  
21 at the totality of environmental exposures in  
22 determining acceptable limits.

1                   The amounts formed endogenously are, to  
2                   a certain extent, a different issue. Ideally, you  
3                   should consider that, also. But we have -- as  
4                   Dr. Krytopoulos has just outlined, that seems to be a  
5                   moving target. And while it might be helpful to make  
6                   an effort to consider these -- again, to provide  
7                   perspective in determining how much concern they give  
8                   to small impurity in a drug preparation.

9                   The net result is that if we start  
10                  giving much different limits for what is consumed in  
11                  food versus what is in drugs, it would seem -- I  
12                  think, to most people, to call the entire risk  
13                  evaluation process into some question. So, I say we  
14                  should not prove it. Thank you.

15                 DR. ATRAKCHI: Thank you, Dr. Rice. I  
16                 just would like to make a -- maybe, one or two  
17                 comments on that.

18                 In foods, in general, we are not  
19                 necessarily ingesting NDMA, NDEA, and other of the  
20                 more potent nitrosamines. We are mostly taking the  
21                 nitrates and nitrites of the food. It is when the  
22                 food is cooked, that is when the nitrosamines are

1 present.

2 In recent dietary assessments -- in  
3 recent study in 2019 and 2020, the amount of -- the  
4 mean NDMA in foods was present at point one parts per  
5 billion. And the total nitrosamines -- there were  
6 about eight of them -- was present at point two three  
7 parts per billion. Very low amounts in foods. And  
8 this is all the result -- I would imagine -- from the  
9 progressive and advancement in food preparation, and  
10 so on, over the last 20 years.

11 So, the amounts from foods, and the  
12 natural amounts in vegetables, spinach, and others,  
13 they are very low. And in terms of calling the --  
14 what we have in drugs -- as very, very miniscule  
15 amounts relative to what we are ingesting, again, I  
16 would like to emphasize that drugs -- we take drugs in  
17 the anticipation that we are taking the active  
18 pharmaceutical ingredient that is responsible for  
19 treating the disease or the illness. We do not expect  
20 the drug product -- or the drug substance to contain  
21 impurities that have no benefit to the -- or  
22 contribution to any benefit to the patient, and into

1 that tablet or pill that we are taking. So, it is a  
2 very different assessment.

3 And, also, we have -- as regulators, we  
4 have GMP quality to follow for what is in a drug. It  
5 is expected. We all expect the drugs to be clean,  
6 pure, as much as possible. So, it is a little bit  
7 different type of assessment.

8 Although, I do agree that -- we all, I  
9 think, agree that we are exposed -- around us, there  
10 is a lot of nitrosamines present. It is all relative.  
11 And I think you have -- you are saying the same thing.  
12 Again, I am not talking about the endogenous. The  
13 endogenous has so many variables. Whether it is the  
14 bacterial colonization, the nitrosation in the gastric  
15 of patients, different than those are who are healthy.  
16 That is not what we are talking about -- what I am  
17 talking about now. It is more of the exogenous  
18 exposure. So, just something to think about. And  
19 then, we can discuss this a little bit more, later on.

20 Dr. Guttenplan, please?

21 DR. GUTTENPLAN: Yeah. I am more of a  
22 laboratory researcher, than involved in regulation. I

1 do not disagree with anything that has been said so  
2 far. I just have one other view point.

3 And that is, suppose one did not have  
4 any exposure, either from exogenous agents, or  
5 endogenous formation. How would one regulate the  
6 nitrosamines that are present in drugs? Would that be  
7 considered a risk, or not?

8 And so, I think that is another way of  
9 approaching the regulation. Suppose we just  
10 disregarded the probably higher amounts that would be  
11 present in the normal dietary intake, and normal  
12 environment of the general population.

13 And that is the extent of my comments  
14 on this.

15 DR. ATRAKCHI: And we do -- I mean, to  
16 answer your question, if we are not going to take into  
17 consideration anything else outside the medicine, then  
18 this will be controlled under what ICH M7 -- and we  
19 have other -- that is for mutagenic impurities. And  
20 we also have other guidance's that are for  
21 regulatory -- for regular impurities that are not  
22 mutagenic. So -- and the complication, here, with

1     nitrosamines, as we all know, is because there are --  
2     we are surrounded, almost, by them, in food and in the  
3     environment. So that is why this question is, should  
4     we take this into consideration. Otherwise, we can  
5     just go and follow some of those guidance's that we  
6     have, and we can calculate the risk/benefit in that  
7     sense.

8                     But that is a very interesting and good  
9     point.

10                    Dr. Bucher?

11                    DR. BUCHER: Thank you. I think I  
12     mentioned this in my response to question three,  
13     yesterday. And I agree. And I think Dr. Kyrtopoulos  
14     laid this out very nicely.

15                    In my view, we should not consider  
16     either the endogenous levels generation, or the  
17     amounts in food and water, with respect to determining  
18     the risks of the incremental increase in risks into  
19     the nitrosamines in drugs.

20                    And I based this upon an argument that  
21     Dr. Kyrtopoulos also mentioned. There is no reason to  
22     believe that somehow the nitrosamines that are being



1 generated endogenously are not carcinogenic. I think  
2 there is a good case that could be made that a  
3 considerable amount of the, quote, unquote,  
4 "spontaneous tumor load," in the population -- which  
5 Dr. Kyrtopoulos correctly indicated runs between 30  
6 and 40 percent -- could be due to contaminating  
7 nitrosamines in our own bodies, generated internally.

8           And if this is the case, then we really  
9 do not have a baseline on which to make a judgment  
10 about how much additional cancer risk could be posed  
11 by even the existing levels of nitrosamine  
12 contaminations in drugs. But we do have ways of  
13 estimating the risks associated with this, using the  
14 TD 50 calculations in the carcinogenic potency  
15 database, that I mentioned yesterday.

16           And I think it is appropriate to go  
17 ahead and use the one in 100,000 risk level as an  
18 acceptable increase risk due to contaminants in drugs.  
19 So, I would be in favor of ignoring, and not taking  
20 into consideration, the background endogenous  
21 formation, or the contributions of exogenous exposures  
22 through food and water, when calculating the risks of

1 nitrosamines in drugs. Thank you.

2 DR. ATRAKCHI: Thank you.

3 Dr. Adamson?

4 DR. ADAMSON: Well, I am with -- I  
5 would be in favor of saying you have to consider the  
6 amounts that are formed endogenously, and the amounts  
7 in food and water. And I want to bring up a point.

8 If you go to a delicatessen, or buy  
9 already cooked ham, or various other cooked things,  
10 those are all are already cooked foods, and probably  
11 have -- despite the fact they probably have an  
12 anti-oxidant in the preparation -- they probably have  
13 a small amount. So, you can buy foods, I think, that  
14 have small amounts of nitrosamines in them, in a  
15 store, in a delicatessen, and other places.

16 So, I think, you also need better  
17 measurements, as has been brought up numerous times,  
18 of the endogenous amounts. But we should also  
19 remember there are other endogenous carcinogens that  
20 contribute to the background. We make a lot of  
21 formaldehyde in our body. We make a lot of ethylene  
22 oxide. We have isoprene. We have a number of other

1 things. They all contribute to the background cancer.

2 And the amount that is present in drugs  
3 that we take, of nitrosamines, is miniscule, compared  
4 to the amount -- and probably adds -- you probably  
5 could not quantify the additional -- if you saying  
6 that 40/50 percent of the population -- let's say 40  
7 percent comes down with some type of cancer, you  
8 probably could not quantify the additional amount. It  
9 is only a number because of risk assessment -- the  
10 addition of five or 10 cases per 100,000.

11 However, we should also remember that  
12 most people, when they get older -- my age, or  
13 starting in the sixth decade -- they are  
14 poly-pharmacy. They do not take just one pill. They  
15 do not something just for blood pressure. They take  
16 something for anti-acid. They take something for  
17 gout. They take something for numerous things. So,  
18 the drugs do give you a benefit.

19 But the amount of nitrosamines, in my  
20 view, should be whatever is feasible, with regards to  
21 also determining the cost of the drugs. So, those are  
22 the three points that I would like to make. We are

1 poly-pharmacy in the drugs. That the endogenous  
2 amounts do -- and food, do overwhelm the amount that  
3 we take as drugs. But we ought to regulate to the  
4 point where it is feasible concerning the cost and the  
5 benefit. Thank you.

6 DR. ATRAKCHI: Thank you, Dr. Adamson.  
7 Dr. Zeiger?

8 DR. ZEIGER: Thank you. Hold on a  
9 second. Unfortunately, there are very good, logical  
10 positions -- logical arguments on both sides of this  
11 issue. And what I keep coming back to is that are our  
12 endogenous exposure -- that any health effects from  
13 nitrosamines would be based on the sum total of our  
14 exposure to nitrosamines, which includes exogenous and  
15 endogenous, as well as what is in the drugs.

16 But, the -- and we know the endogenous  
17 exposure is highly variable -- is affected by diet, by  
18 the genetics, by lifestyle, and many things. But  
19 everything contributes to the additivity of the  
20 response. And so, to some extent, this implies a need  
21 for more concurrent accurate -- more current, accurate  
22 human data on endogenous formation.

1 But even if the incremental increase is  
2 miniscule, I think a good argument can be made for  
3 considering the endogenous and exogenous -- other  
4 exogenous exposures to it.

5 You know, that said -- you know, it may  
6 not make a difference. You know, the added exposure  
7 from the drugs may not affect the overall risk  
8 assessment for that particular nitrosamine, or for the  
9 nitrosamines in summary. And I think maybe that would  
10 be a way to address it. What is the potential  
11 risk -- tumors per 100,000 -- cancers per 100,000  
12 based on the exogenous plus the added drug. You know,  
13 showing there may be no difference, or there may be a  
14 difference. We do not know. But we just need more  
15 data on the endogenous levels.

16 But we cannot just say that -- you  
17 know, saying just looking at the -- what is in the  
18 drug, we cannot just say that, that is our only risk  
19 factor. Somehow, we have to include any  
20 communications on risk -- any calculations on risk,  
21 based on the total exposure. Whether that total  
22 exposure is just one percent more than the endogenous,

1 or 10 percent more than the endogenous.

2 But as I said in the beginning, one can  
3 make a good case for either approach, looking only the  
4 drug levels, or looking at the total exposure levels.

5 Thank you.

6 DR. ATRAKCHI: Thank you.

7 Dr. Hecht?

8 DR. HECHT: Right. Well, we have very  
9 good data on nitrosamines in food and the exogenous  
10 exposure, particularly for the more common  
11 nitrosamines, like dimethyl and dimethylnitrosamines.  
12 So, we can really use that data in part to address  
13 this question of additional risk, as all the other  
14 speakers have mentioned. And chances are that the  
15 levels that you get of dimethyl and  
16 dimethylnitrosamine -- where we have a lot of good  
17 data -- from pharmaceuticals are probably quite low  
18 compared to the diet. But -- you know, the  
19 calculation has to be made.

20 But we do not have good data, in my  
21 opinion, on endogenous formation. It may very well be  
22 that the endogenous levels that are formed, are really

1 far greater than the amounts that you are exposed to  
2 through drugs -- as are also -- already been  
3 suggested. But I really do not think we have very  
4 good data on that.

5 And the other thing we have to consider  
6 are the structures of the nitrosamines. Most of what  
7 we have been talking about -- and a lot of the data in  
8 food is based on dimethyl and dimethylnitrosamine.  
9 But many of the structures of the nitrosamines that  
10 are found in drugs are quite different from that. So,  
11 I am not sure that we can actually make a blanket risk  
12 assessment by considering all nitrosamines at the same  
13 level of risk, because they have different biological  
14 activities.

15 In essence, I think that in some cases  
16 the nitrosamine exposure in drugs can be avoided by  
17 careful monitoring of the manufacturing process. And  
18 I do not think we should get into the situation where  
19 we are saying, oh, well, it does not matter because --  
20 you know, you get so much exposure from food,  
21 that -- you know, so what if we generate some  
22 nitrosamines in the drug manufacturing process. No.

1 This is not correct. In most cases, the generation of  
2 nitrosamines during the manufacturing of the active  
3 pharmaceutical ingredient can be avoided by using  
4 correct chemistry.

5 That is all I have to say.

6 DR. ATRAKCHI: Thank you, very much,  
7 Dr. Hecht.

8 I would like to see if anybody else on  
9 the panel, who would like to add to this question?

10 DR. EISENBRAND: I would like to add a  
11 little bit more to that. If I am allowed.

12 DR. ATRAKCHI: Absolutely.

13 DR. EISENBRAND: I cannot agree more  
14 than with what Steve Hecht said. I think it is really  
15 important to recognize that we have a relatively solid  
16 database, in terms of exogenous exposure for food.  
17 And that is why I think it is a pragmatic process to  
18 take this as a point of reference. Mainly, because we  
19 do not really know how high or low the risk of the  
20 endogenous exposure side is. But this, of course, is  
21 a matter of future research.

22 But, Dr. Atrakchi, you brought a very



1 interesting point into the discuss. And that is the  
2 good manufacturing practice. And if we -- you know,  
3 leave a little bit at the moment, the discussion about  
4 the potential risk aside, and just concentrate, as --  
5 by -- also said, just now -- on the good manufacturing  
6 practice, then we can say, well, according to good  
7 manufacturing practice, we can produce drugs  
8 without -- or with an extremely low miniscule  
9 contamination by n-nitroso compounds. And that,  
10 actually, would be, in my opinion, a good way out.  
11 Just concentrate on this. We did this in Europe  
12 before, for the cosmetics. Where it was realized that  
13 the exposure after mitigation measures had been taken,  
14 really approached miniscule amounts. So, we could  
15 concentrate on the good manufacturing principals, and  
16 say, well, according to good manufacturing principals,  
17 you can avoid nitrosamines conditions in the  
18 environment or in the fabrication environment, and so  
19 on, and can come down to limits that should not be  
20 exceeded. And that, I think, is a good way out, if we  
21 take this as a measure to follow.

22 But I think one point that should not

1 be forgotten, is that we also have a potential risk of  
2 endogenous formation of nitrosamines compounds from  
3 drugs. So, if you have, for instance -- the drug is  
4 really clean, but that has a structure that cannot be  
5 nitrosated endogenously, then we need to avoid that  
6 risk. And that is why it is now almost 40 years ago  
7 that WHO introduced this nitrosation as a procedure,  
8 just to get a rough measure about the nitrosatability  
9 of drugs. And this, I think, should not be forgotten  
10 -- that we also have to take this into consideration,  
11 in terms of regulation, as well.

12 Thank you, very much.

13 DR. ATRAKCHI: Thank you.

14 Dr. Keire?

15 DR. KEIRE: Yeah. I guess, I -- you  
16 know, when this nitrosamine -- when the nitrosamine  
17 started showing up in drugs, a lot of us at the FDA --  
18 you know, were thinking along the lines of, well,  
19 okay -- you know, what is the level of exposure from  
20 drugs relative to diet, and -- you know, we got in  
21 contact with our colleagues at CFSAN, we dug into the  
22 literature, and a couple things strike me from that

1 whole process.

2                   One is -- and I think it has, kind of,  
3 been referred to already -- that there is quite a wide  
4 range of values for the exposure from diet to  
5 nitrosamines. I mean, and -- you know, you might  
6 expect some level of variability because of the diet  
7 you might eat in South Korea, versus -- you know, a  
8 western diet, versus -- I do not know -- a lot of  
9 sausage in Denmark -- whatever it is. You know that  
10 there is a range of what you might consume in a given  
11 country.

12                   And then, also, there is this aspect of  
13 the different measurement. And I think that there is  
14 a complexity to making measurements where you are --  
15 you have to make sure that you are not adding  
16 nitrosamine in the process of making the measurements,  
17 right -- either from the preparation of the sample, or  
18 the measurement technique itself.

19                   And so, I guess, I think I want to  
20 propose that I think there needs to be better data,  
21 right -- and newer data. And maybe with a  
22 standardized processes across many diets, right? The

1 drugs go in -- are distributed globally in lots of  
2 different populations with many different diets. And  
3 so, we really want to try to regulate -- you know,  
4 like, exposure to nitrosamines, you really have to  
5 think of it globally, across all those diets. And  
6 then, I guess, trying to come up with values, based on  
7 different measurements techniques, with -- you know,  
8 unknown suitability for the particular measurement.

9           You know, all these questions came up  
10 in that process. And so, I think it is a really  
11 difficult landscape to make a judgment about -- you  
12 know, what is the real level of exposure. And I think  
13 it does need a new focus.

14           As well as -- you know, the endogenous  
15 measurements -- you know, I think there needs to be  
16 better -- new and focused measurements that are doing  
17 this in the careful way. Again -- you know, down at  
18 this parts per billion level -- you know, trace  
19 measurements are -- can be challenging to do  
20 correctly -- you know, because of contamination  
21 issues, or other issues. So, I think there really is  
22 a need for good data with -- or new data with

1 standardized methods across many diets, to get a real  
2 baseline value. Thank you.

3 DR. ATRAKCHI: Thank you. And this is  
4 assuming that -- I mean, we did get a little bit  
5 different opinions -- or approaches, in the sense  
6 that, yes, we do need to take into consideration the  
7 diet and the exogenous exposure. But certainly, we  
8 also heard that, maybe, that should not be considered  
9 if we are simply, based on -- you know, we need the  
10 quality drugs, and when possible, these nitrosamines  
11 should not be present in drugs.

12 So, it is all relative. And it is all  
13 important things to take into consideration.

14 I do like to -- there was as discussion  
15 from yesterday that -- about this endogenous exposure  
16 in the past, versus the current situation. And I  
17 believe Dr. Eisenbrand, and Dr. Kyrtopoulos mentioned  
18 that there were good data -- very good -- there are  
19 good data that -- evaluation -- to update the  
20 evaluation of exposure to endogenous levels of  
21 nitrosamines. Can they -- can we use -- assuming the  
22 endogenous exposure is primarily driven by diet, is it

1 reasonable to use the current dietary intake levels in  
2 comparison to the past assessments to make a similar  
3 adjustments from those past measurements, until we get  
4 more of this new data that we can collect in the  
5 future? Can we extrapolate from those to the current  
6 status?

7 Anyone -- would like to comment?

8 DR. HECHT: Yeah. I --

9 DR. DINOVI: Dr. Atrakchi, it is  
10 Mike -- oops. Sorry.

11 DR. HECHT: Okay. Go on.

12 DR. DINOVI: Do you mean levels of  
13 nitrate and nitride in food now, versus the past?

14 DR. ATRAKCHI: Well, yeah. I mean,  
15 there was a discussion yesterday, that where there are  
16 a lot of -- there are good data from a while ago,  
17 where endogenous levels have been measured and  
18 determined, but they are old. And we need -- based  
19 on -- things have changed. The dietary -- how we eat,  
20 and what we eat, also, slightly have changed. So can  
21 we use the previous -- and everybody is telling us  
22 that we need more current information -- current

1 measurements of the endogenous levels compared to the  
2 past. But this will take some time. Can we use the  
3 old data and extrapolate from that for the current  
4 time, to see where we are in those amounts and  
5 measurements? Nitrates are -- obviously, we are -- it  
6 is mostly nitrates and nitrites that we are -- that  
7 are present in the diets. And the nitrosamines are  
8 present, but at very, very low levels in the fresh  
9 fruits and the fresh vegetables.

10 Did I --

11 DR. DINOVI: Yeah. Nitrate exposure is  
12 a thousand times higher than nitrosamine exposure.  
13 That is for sure.

14 DR. HECHT: Sure. I have some data on  
15 that.

16 DR. ATRAKCHI: Go ahead, Dr. Hecht.

17 DR. HECHT: Yeah. There was quite a  
18 bit of work some years ago on endogenous formation of  
19 nitrosoproline. It has been discussed yesterday. Of  
20 course, nitrosoproline is excreted unchanged, and it  
21 is not metabolized at all. So, the -- it is a good  
22 monitor of endogenous formation. And Mirvish, and

1 colleagues carried out a series of studies where they  
2 measured the amount of nitrosoproline in the urine of  
3 people who had ingested -- as an example, 400  
4 milligrams of nitrate and 500 milligrams of proline.  
5 And this yielded about nanomoles of nitrosoproline in  
6 urine. That is a yield of point six times 10 to the  
7 minus third percent. So, that -- and I think that  
8 data is reliable. There is a lot of other data on  
9 nitrosoproline from 20 years ago, or so, that, I  
10 think, are quite reliable.

11 So, that gives you an idea of the  
12 extent of endogenous formation in one relatively  
13 favorable circumstance.

14 DR. DINOVI: So that is a very low  
15 conversion percentage, right?

16 DR. HECHT: Correct.

17 DR. DINOVI: Yeah. That is  
18 interesting. Thank you.

19 DR. ATRAKCHI: Thank you. Anyone else  
20 to comment on this?

21 DR. ZEIGER: Yes. You know, we have  
22 known for many years that diet -- you know, has a big



1 effect on cancer incidents. So, if we are going to do  
2 any studies on endogenous formation, maybe, they  
3 should be done -- not just take a few hundred people  
4 and measure it, but set it up, almost, as an  
5 epidemiology study. We are looking at effects of  
6 diets and different dietary regimes on nitrosamine  
7 formation. You know, vegetarian versus meat  
8 eater -- people high levels of fish -- people eating  
9 high levels of fruits and vegetables. You know,  
10 because this will all of -- this -- all of this will  
11 effect whatever endogenous levels we have. So, to  
12 just measure random -- people at random, I think will  
13 not give a fairly good range -- or fairly accurate  
14 range.

15 DR. EISENBRAND: Yeah. That has  
16 been -- actually, that has been carried out quite a  
17 bit -- this epidemically logical research by European  
18 and -- groups and also by groups in the United States.  
19 And -- you know, the main -- one of the main questions  
20 was -- that you have the highest levels of nitrate,  
21 you have in vegetables -- certain vegetables are  
22 really high, because they just accumulate nitrate.

1 And so, the highest intake of nitrate comes definitely  
2 from consumption of vegetables. However, fresh green  
3 vegetables have a protective associated -- at least,  
4 the consumption with a protective -- for instance,  
5 what mainly has been in focus in these investigations  
6 on colon cancer incidents. So, colon cancer incidents  
7 is -- there is a low incidence associated with  
8 enhanced consumption of green vegetables.

9 If you would think that nitrate in this  
10 case plays a role, then one has, really, to  
11 reconsider -- and has been reconsidered that. Because  
12 a possible explanation is that many anti-oxidative and  
13 inhibiting agents -- inhibiting to the n-nitrosation  
14 reaction, are also co-consumed in green vegetables,  
15 like phenolics and many other vitamins -- vitamin C,  
16 vitamin D, and so on -- and B.

17 So, that is the reason. And that is  
18 why I think the whole subject of endogenous formation  
19 is really very complex, and really, very complicated.  
20 It is not a simple way to really come to a point where  
21 you can say reliable, this endogenous formation is x  
22 times higher than what you get from exogenous

1 exposure. The suspicion is quite realistic that it is  
2 that way. But it is so many complex inference  
3 parameters going on, including the physiological state  
4 of the people -- the health state of the people --  
5 inflammatory situation -- infections, and all these  
6 things that drive the formation -- the endogenous  
7 formation of nitrate.

8 And that is the main reason why I think  
9 that we have the best and most reliable data density  
10 with the analytics of the exogenous formation -- the  
11 exogenous occurrence of nitrosamine components in  
12 food. And I would, of course -- as I said yesterday,  
13 I think it is a good idea to re-check this -- to  
14 re-visit these levels. My suspicion is that they are  
15 even lower today. But it should be -- of course, it  
16 needs to be measured again -- the actual data as they  
17 are -- yeah.

18 But, still, I think the argument -- the  
19 most -- main argument is that we have a much bigger  
20 data density -- of good data, also -- despite of  
21 the -- all the analytical problems that have been  
22 mentioned, already by Dr. Keire.

1 But there are good data, because many  
2 of the more recent surveys have been carried out  
3 with -- especially, proof against artificial formation  
4 of nitrosamine components during analysis.

5 DR. ATRAKCHI: Thank you. Dr. DiNovi,  
6 would you like to comment on this -- in particular,  
7 what Dr. Zeiger was saying about conducting  
8 epidemiological studies on the -- what the diets and  
9 what people eat, and so on, and more controlled than  
10 just simply taking random. My understanding with  
11 CFSAN, you have fairly interesting software that where  
12 you can choose and determine what -- down to what a  
13 person -- how much a person can eat -- let's say a  
14 specific type of cheese and determine the content of  
15 whatever it is we are looking for -- whether it is  
16 nitrosamine, or something else -- fairly interesting  
17 models that CFSAN uses.

18 DR. DINOVI: Yeah. In fact, the  
19 numbers that you quoted earlier -- when you were  
20 talking about the exposure, came from work that one of  
21 my colleagues did -- Dr. Lee -- he is listed in the --  
22 his papers are listed in the references. So, people

1 can take a look at those.

2 And the other thing that -- I mean, we  
3 do not do epidemiology type studies, at all, in my  
4 office -- and somewhere in the Center for Food Safety  
5 there are epidemiologist. But it is not us. The one  
6 thing that we do, do, that is related to what we are  
7 talking here, is we can look at time course of  
8 intake -- our food consumption databases go back, at  
9 least, to the late 90's. So, you can look at 20 years  
10 of data, and look at the trends and see if it is going  
11 up and down. So that is a question we can answer  
12 fairly easily -- whether or not nitrate -- and I am  
13 going back to nitrate and nitride level, which are --  
14 you know, easier to get. That, we can take a look at.

15 But I do want to comment on one of the  
16 other questions -- and it is about the confounding  
17 things when you look at in vivo stuff. For  
18 example -- and I am just taking a look at some of  
19 Dr. Lee's data, here -- the single highest food  
20 sources for pre-formed nitrosamines are smoked meats,  
21 smoked fish, pureed and grilled meats. And the  
22 problem there is, all those, also, are

1 significant -- take that word with a grain of salt,  
2 but there are all good sources of polyaromatic  
3 hydrocarbons, and other carcinogens. You know, we, in  
4 the food world, know that grilling food makes it taste  
5 great, but it is also much more, air quote,  
6 toxicologically dangerous than boiling, steaming, or  
7 microwaving your food, right? So those things would  
8 have to be taken into account if you want to take a  
9 look at any of those things and see if you can tease  
10 out the nitrosamine contribution to whatever  
11 carcinogen -- carcinogenic endpoint you were looking  
12 at. But certainly, we would be more than happy to  
13 contribute to looking at these time courses of these  
14 things.

15 From a purely numeric point of view,  
16 thought, it is probably -- no -- I am going to go  
17 beyond probably -- it is certainly less than an order  
18 of magnitude change, if it is changed at all.

19 Thank you.

20 DR. ATRAKCHI: Thank you.

21 Dr. Kyrtopoulos?

22 DR. KYRTOPOULOS: Yes. Thank you. We

1 certainly have very good data on nitrosoproline  
2 excretion. I think these are the data we were  
3 mentioning in your introduction earlier, that -- we  
4 have reliable ES measurements and lots of studies.

5           What the nitrosoproline studies really  
6 told us, referred to -- concerned the conditions which  
7 influence endogenous nitrosation. They told us what  
8 the hosts capacity -- of different hosts, depending on  
9 the shelf conditions, and so on -- how they influence  
10 endogenous nitrosation. They told us about what  
11 intakes influence nitrosation, and so on. However, in  
12 the context that we are discussing now, I think that  
13 what -- which has to do with the role of endogenous  
14 exposure and how it should be assessed in the context  
15 of overall risk assessment for a particular  
16 chemical -- let's say NDMA -- here, we need studies  
17 which will somehow -- I do not exactly how that would  
18 be achieved -- give us reliable data on the endogenous  
19 formation of the particular compounds.

20           So, I can certainly see the weakness of  
21 what we have now, in terms of the analytical  
22 reliability of the data -- whether there may be

1 concentrations of NDMA in urine and blood, which are  
2 very old measurements -- or DNA adducts, whose  
3 shortcomings I mentioned yesterday. And I know  
4 that -- I believe that today we have -- we do have the  
5 technical capability to acquire much more reliable  
6 numbers. So, I think this is what we need, now, in  
7 order to be able to answer the questions that we have  
8 been asking. How serious is the endogenous burden of  
9 a particular nitrosamine towards the overall cancer  
10 risk. And, I think, for this, we need proper  
11 measurements. And I agree that they have to be done  
12 once we have set up the systems and we have found the  
13 proper design of the studies. I think we need, kind  
14 of, epidemiological studies, because it is very clear  
15 that we understand very little -- the determinants of  
16 endogenous nitrosation. We do not really have time to  
17 discuss this in detail, now. But I mean, there are  
18 papers in the literature where people try to give --  
19 for example, anti-oxidants, inhibitors of  
20 nitrosamines -- ascorbic acid, or other chemicals --  
21 and they saw results, which were not always what they  
22 had anticipated. They deviated from what one would



1 have predicted in one way or another.

2 So, I think the system -- this system  
3 of in vivo nitrosation is affected by a lot of  
4 factors, which we do not understand. So, until we get  
5 to the point where we can understand them, what -- if  
6 I had the technical capacity -- in other words, the  
7 right instrumentation to measure reliably what I want  
8 to measure, I would just collect a -- you know, a  
9 population of people, and measure what -- estimate --  
10 carry out my estimation of endogenous nitrosation.  
11 And then, try to make sense of what the determinants  
12 may be, and what we -- the range of endogenous  
13 formation, and so on.

14 Thank you.

15 DR. ATRAKCHI: Thank you, very much.  
16 Any other comments from the panelists?

17 DR. GUTTENPLAN: -- yeah.

18 DR. ATRAKCHI: Yes?

19 DR. GUTTENPLAN: In a way, maybe,  
20 repetitive, but I think from what we talked about  
21 yesterday, we are below the threshold for  
22 non-linearity with exogenous and endogenous

1 nitrosation. So -- and the result -- the  
2 carcinogenicity and genotoxicity of nitrosamines is  
3 additive under these conditions. One should be able  
4 to calculate, then, an incremental affect of the  
5 nitrosamines and the drugs, irrespective of the  
6 endogenous and exogenous exposure, resulting in  
7 nitrosamines.

8 It is probably not measurable because  
9 it is such a small difference compared to what is  
10 there. But it should still be calculable.

11 So that is repetitive. But that is one  
12 way of looking at it.

13 DR. ATRAKCHI: Thank you. Anyone else?

14 DR. EISENBRAND: Just to state that I  
15 am totally in line with what Dr. Kyrtopoulos said. I  
16 think the -- going into the research to really address  
17 and quantify, wherever possible, the endogenous  
18 nitrosation potential, is very, very important for the  
19 future. But it is, in my opinion, quite, a big task.  
20 It is not really trivial. But we have -- today, we  
21 have the records and the means to approach that -- and  
22 I think it is very important to get quantitative

1 figures. But we do not have them, now, at the moment.  
2 At least not reliable ones. We have indication that  
3 there is, perhaps, substantially vivo formation, which  
4 may be exceeding the ex vivo exposure quite a bit --  
5 the exogenous exposure quite dramatically, perhaps.  
6 But we need to confirm that. We need to really check  
7 it, re-check it, have the right methods to measure it.  
8 So, this will be an undertaking that will take time.

9 And for the time being, as I said  
10 already -- and I do not want to repeat me, again -- I  
11 think a good way of putting the endogenous potential  
12 of formulation of nitrosamine components in  
13 perspective to the exogenous exposure, or the diet.

14 And the other point I would like to  
15 make again is that, if we have good manufacturing  
16 practice rules set -- technically, to produce drugs  
17 without -- or with very, very low nitrosamine  
18 contamination, we should do that irrespective of a  
19 risk consideration, in my opinion. That, as I said,  
20 we did that for the cosmetics in Europe.

21 DR. ATRAKCHI: Thank you, very much,  
22 Dr. Eisenbrand. I think you -- I was about to more of

1 less summarize what seems to be the answer -- or  
2 comments on this question. But you just did it very  
3 nicely.

4 Mainly, overall, I believe is that it  
5 is very important to determine accurate the endogenous  
6 formation of nitrosamines. But this is require --  
7 will require time and fairly sensitive and highly  
8 sophisticated analytical methods. And that should eb  
9 done -- need to be done. But it is in the future.

10 In the meantime, consideration for  
11 exogenous exposure to nitrates, nitrites, and other  
12 sources, as well as nitrosamines, that -- we have data  
13 from the past, and we could more or less reliably use  
14 some of this information, as well as, not terribly old  
15 data. However, more going back to the GMP, it comes  
16 down to the chemistries, and to the manufacturing.  
17 So, we do need, with respect to pharmaceuticals, and  
18 medicines, and drugs, to start with -- it is really  
19 the chemistry and the controls of the manufacturing  
20 that needs to be considered, until all these data are  
21 collected. Then, we can compare what is the levels  
22 that we ingest on a daily basis from the environment

1 around us, versus what is present in medicines.

2 If anybody disagrees with this quick  
3 summary, please go ahead and -- I know there were  
4 different opinions of how to do this, or -- but I  
5 think the overall -- there is pros and cons to both.  
6 Whether it is the exogenous, the endogenous exposure,  
7 as well as what is in the drugs, ultimately it is the  
8 drugs need to be under control for GMP for any types  
9 of impurities. And in this case, particularly for  
10 nitrosamines.

11 If no other comments, I would like to  
12 go to question six. Okay.

13 So, now we move to the chemistries of  
14 nitrosamines. Question six is one of two chemistry  
15 questions. In the absence of data and based on  
16 identified differences in nitrosamine chemistries and  
17 reactivities, can read-across for structural similarly  
18 to related compounds be used for nitrosamines? What  
19 are the key parameters to consider when conducting  
20 QSAR assessment for nitrosamines?

21 There has been a tremendous advancement  
22 of in silico modeling and software engineering to

1 predict many aspects of biology and chemistries,  
2 including chemical structural similarity. With a  
3 diversity of nitrosamine behaviors, both in vitro and  
4 in vivo, what are the pros and cons, and what is the  
5 extent of reliability for using QSAR to predict  
6 nitrosamine mutagenicity and/or their reactivity?

7 I would like to start with Dr. Cronin.

8 DR. CRONIN: Thank you. And there has  
9 already been a lot of discussion of chemistry and  
10 structural activity right from our first lecture  
11 yesterday, from Professor Eisenbrand. And let's just  
12 think for a moment why we want to do that.

13 And the advantages of going to  
14 structural activity, read-across QSAR, that in theory,  
15 at least, it is quick. It should be cheaper than  
16 doing, certainly, the longer-term animal tests. And  
17 it may not require animals.

18 You know, disadvantages; these are  
19 predictions, these are inferences, so we do have less  
20 certainty. And especially when we come to use  
21 read-across, we need some expertise. And already  
22 listening to the discussion in the last day or so, I

1 really appreciate the expertise already in this area.

2 My background is in, in silico  
3 toxicology. And I have taken the opportunity in the  
4 last couple of weeks to get a feel -- or refresh my  
5 opinions and understanding of this particular area,  
6 with regard to nitrosamines. There is a lot that has  
7 been going on. Particularly, very recently. And I am  
8 going to try to capture some of that, and, also bring  
9 together some of the information that we have already  
10 had.

11 Now, the question asks about  
12 read-across and QSAR, and I am going to deal with  
13 those separately. And I am going to start with  
14 read-across. And for those of you not familiar with  
15 the term, very briefly, read-across -- we are trying  
16 to infer an activity -- here, it might be the  
17 toxicity -- and that could be ultimately the  
18 carcinogenicity, or even a potency. We are trying to  
19 infer that for a molecule we may not know very much  
20 about -- or very little about -- from a similar  
21 molecule that is data rich -- or indeed a group of  
22 molecules that are data rich. And we have got a lot

1 of expertise in this, going back -- well, at least, 30  
2 years -- and particularly with regard to regulatory  
3 use of read-across, and more specifically, probably in  
4 the last decade, how we can accept this, and the  
5 uncertainties associated with that. And I am thinking  
6 particularly of what has happened in Europe with  
7 REACH. But there is lots of other examples in the  
8 U.S. and Canada, and elsewhere in the world.

9 And read-across, itself, covers a  
10 number of techniques, which particularly in the last  
11 decade have been developed quite considerably,  
12 starting with the simple use of analogs -- and I will  
13 discuss that in a moment -- through to what we mean by  
14 chemical similarly.

15 So, I think there are three issues we  
16 need to think about with read-across, that are going  
17 to be immediately important for you for nitrosamines.  
18 And firstly is, what do we mean by data rich  
19 molecules? And, here, we have this term where we want  
20 to infer from data rich molecules, and actually -- as  
21 we have heard -- we are probably quite lucky for the  
22 nitrosamines, compared to many other chemical classes,



1 as we have many carcinogenic data supported by  
2 mutagenetic data publicly available, and available  
3 within corporate and regulatory arenas.

4 There are some really nice reviews in  
5 this area. There is a very good review, recently, in  
6 2020, from Andrew Thresher, from Lhasa Limited, who  
7 takes you through the carcinogenic and mutagenic data,  
8 and as well, I am aware of the ad hoc working group  
9 led by LeadScope and Lhasa in this area.

10 In doing some background, I had looked  
11 at the publicly available resources. We have already  
12 heard reference to Lhasa Limited CP DB website. I  
13 just put a nitrosamine structure in there, and I got  
14 140 structures out associated with carcinogenic data,  
15 to give you some idea of the data resources.

16 I also searched nitrosamines in the  
17 OECD QSAR tool box. And there are several hundred  
18 publicly available mutagenic data. And you will get  
19 these from -- or those kind of numbers from other  
20 resources. For instance, the US EPA chemistry  
21 dashboards, maybe ChEMBL and PubChem, as well.

22 And I also realize there is probably a

1 lot of data that have been made available -- or are  
2 available and could supplement the publicly available  
3 data from corporate backgrounds. I know the -- or I  
4 suspect the Lhasa LeadScope initiative has been able  
5 to tap in those.

6 So, with regard to data, therefore, we  
7 have many potential so-called data rich source  
8 molecules that we can read-across from. That gives us  
9 a strength -- or a position of strength.

10 The thing I would say, where are the  
11 data? Are they in a format that you can use easily  
12 for read-across? Are they in a correct informatics  
13 type format. The tool box -- the OECD QSAR tool box  
14 is one way of doing that. But may not be ideal for  
15 all sorts of purposes. So, FDA may need to think  
16 about how they are going to use those particular data  
17 resources.

18 Second issue with read-across is the  
19 concept of similarity. And similarity really is a  
20 very, very subjective opinion about whether two  
21 molecules are similar or not. And I know we have  
22 measures of similarity. But at some point, you are

1 going to have to make a decision that something is  
2 suitably similar, that you can have confidence in  
3 reading-across your toxicity.

4 We have got loads of guidance. There  
5 is lots of guidance -- for instance, from OECD, EFSA,  
6 ECHA, US EPA, and various industry bodies. And they  
7 give us several ways of defining how we can identify  
8 similar molecules.

9 For nitrosamines, the obvious way of  
10 doing this is saying it has the n-nitrosamine  
11 structure in it. But in practice, that would be too  
12 crude a measure to do read-across from. So, we need  
13 to undergo a process of sub-categorization. And that  
14 allows us to be quite discriminatory -- or it gives us  
15 the opportunity to be more discriminatory, at least.  
16 And to do that, we probably want to pull in our  
17 knowledge of reactivity, our knowledge of chemistry,  
18 and go to the data and get this information structural  
19 activity from the data.

20 So, again, I really appreciate some of  
21 the work that I have seen very recently from the ad  
22 hoc group. It was presented by LeadScope at SOT, a

1 couple of weeks ago -- to identify many of these types  
2 of structural activity relationships and put them into  
3 terms of structural alerts. And particularly, potency  
4 alerts can be based around chain lengths, substitution  
5 on the alpha and beta carbons, electron withdrawing  
6 groups, and so forth.

7 So, now, we can go from just a  
8 nitrosamine structure, through to much more subtleties  
9 about structural activity. And that really links in  
10 structural knowledge, to reactivity, to our  
11 understanding of mechanisms of action.

12 Final aspect of read-across, which has  
13 probably caused the most problems in Europe, in terms  
14 of REACH, is the justification of read-across. So, in  
15 other words, we build a category, we have identified  
16 analogs, we do the read-across, but then, we have to  
17 justify why that is acceptable.

18 We are back around into this -- the  
19 previous argument about structural activity, is, of  
20 course, a fantastic basis to start from. And we are  
21 also doing things like supplementing our arguments  
22 with new approach methodology and NAM type data. It

1 would be in vitro data, further in silico data, and  
2 chemico data. So therefore, maybe, if required  
3 possible to supplement these read-across arguments  
4 with a relatively small number of quite cheap, rapid  
5 tests to help us understand similarity, help us  
6 justify a hypothesis.

7 The reality I am learning is, it is --  
8 we have greater certainty -- or we have less problems  
9 with certainty if we are reading across a positive, a  
10 strong carcinogen in this case. You are going to need  
11 more evidence, in reality, to be able to read-across a  
12 negative, or low toxicity compound. And we heard the  
13 argument yesterday at the end of the session about  
14 what happens if you have Ames negative compounds.

15 And the benefits of read-across, I  
16 think it gives you an ability to test hypotheses. And  
17 we heard again -- going back to the -- if we have a  
18 negative Ames test, we can then test hypotheses --  
19 well, what do we know around that area of chemistry?  
20 What would we expect? Does it all fit together? And  
21 it gives us a rational way of organizing data. So, we  
22 are not just dealing with molecules, necessarily, in

1 isolation.

2 Moving onto QSAR, and more formally  
3 that is quantitative structure-activity relationships.  
4 And those -- there is a continuum from where  
5 read-across finishes and QSAR starts, it must be said.  
6 But they are more commonly thought of quantitative  
7 predictions on the basis of physical chemical  
8 properties structural descriptors. And they can be  
9 very, very varied. Clearly, we do not have time to go  
10 into the full gambit, here. But they can go from a  
11 very small number of molecules -- basements and some  
12 regression analysis -- which is where we started in  
13 the area -- right the way up to a very large number of  
14 molecules -- big data types of molecules where in we  
15 have to use -- and go up to machine learning --  
16 artificial intelligence type methods.

17 For nitrosamines, I think we want to  
18 focus in on the smaller and more subtle types of  
19 models. I cannot see -- we do have large global  
20 QSARS -- as I call them -- coping with -- or including  
21 many types of molecules and many types of affects.  
22 But I think they will struggle with nitrosamines for

1 the subtleties we know that are in the chemistry and  
2 the activity cliffs.

3 So, my recommendation for QSARs -- if  
4 we are going to build them around -- for instance TD50  
5 values, which would be very complex -- or mutagenic  
6 data -- would be to just look at nitrosamines as a  
7 group -- as the largest group -- and maybe even in --  
8 to focus in on some of those structural activity  
9 relationships, and build quantitative models, there.

10 With regard to the kinds of descriptors  
11 that we are going to use -- well, I am a biologist,  
12 and I believe in mechanisms, and I believe our models  
13 should be relatable back to mechanisms of action, and  
14 also understandable. So, the question to ask  
15 ourselves is -- well, what is controlling the activity  
16 that we are trying to model?

17 Clearly, I have seen some relationships  
18 and QSARs attempted for -- to simply trying to  
19 correlate TD50 to log P. And without any surprise  
20 whatsoever, those relationships do not exist. So, it  
21 is more than our classic log P parameters. And of  
22 course, it must related in some ways to reactivity.

1                   So, we need to think how we can  
2     parameterize reactivity. And I have not seen any good  
3     published QSARs in this area that they -- there may be  
4     some available. But surely, we can do quantum  
5     chemical level calculations to understand and model  
6     those particular steps that we know are controlling  
7     potency.

8                   So, the last thing I would like to say  
9     about QSAR is, in terms of formulating the model  
10    itself -- and QSAR works best when you have a large  
11    variation of activity, going over several orders of  
12    magnitude. And ideally, that we have got a spread of  
13    data across that, so we can form a strong model. What  
14    I fear may be the case with QSARs for this -- for  
15    nitrosamines is, we have heard, repeatedly, we have  
16    got a lot of high potency nitrosamines. So, you may  
17    get a situation where you have a large group of  
18    data -- which are high potency, and then, relatively  
19    fewer data, which are lower potency. And this gives  
20    us some problems in modeling. There are ways around  
21    it. But just be very cautious with that.

22                   So, to summarize, given the model and



1 given the problem of nitrosamines, given the current  
2 data resources and mechanistic knowledge, I think you  
3 can do read-across, you can do QSAR. My preference  
4 would be structural activity based rational  
5 read-across supported where possible by the data we  
6 have. And that is my comment for the moment. Thank  
7 you.

8 DR. ATRAKCHI: Thank you, very much.

9 Dr. DiNovi?

10 DR. DINOVI: So, I have to admit this  
11 is not my field, so I really -- I cannot say too much,  
12 here. But I certainly would not disagree with  
13 anything that I just heard. So, thank you.

14 DR. ATRAKCHI: Thanks.

15 Dr. Bucher?

16 DR. BUCHER: So -- well, I want to  
17 compliment Dr. Cronin. He has really done a terrific  
18 job at capturing the complexities and I must say,  
19 the -- his predictions about the issues related to  
20 read-across and QSAR models with respect to  
21 nitrosamines mimic, I think, our thinking, and what we  
22 have been able to do just in looking at this problem

1 over the last couple of weeks. Recognizing that  
2 people have been working in this area for 40 years,  
3 now, and trying to come up with good models to -- for  
4 classifying and predicting potency for various  
5 nitrosamines.

6 We have been looking at this only for a  
7 couple of weeks. So, I challenged our chemo  
8 informaticist, here, in the program, Dr. Kamel  
9 Mansouri, just to take a quick look at this, applying  
10 some of the new tools with machine learning, and  
11 something called the OPERA database, as a database of  
12 predicted physical chemical properties, and  
13 cross-referencing that to the carcinogenic potency  
14 database, and the loss of data what was just  
15 discussed. And it is very preliminary efforts. He  
16 was able to generate some predicted TD50s -- or  
17 potency estimates that did look reasonable, applying  
18 these machine learning and multiple regression models  
19 to the QSAR data and physical chemical properties.  
20 And as I said, incorporating the carcinogenic potency  
21 database numbers. He did this looking at the TD50's  
22 for over 700 substances in the database that have QSAR

1 ready data -- if you will -- and rodent TD50 data.  
2 And he also did this in models that were restricted  
3 only to the -- about 120 nitrosamine -- the rodent  
4 data TD50s, as well. And what he found is exactly  
5 what Dr. Cronin predicted.

6 The results of the five-fold cross  
7 validation studies that he did were somewhat  
8 promising, but the models needed additional work to  
9 better discriminate the very potent carcinogens -- the  
10 very potent nitrosamines, from ones that would be  
11 considered weak or negative. Additional information  
12 from the mutagenicity studies -- or QSAR and physical  
13 chemical properties for non-carcinogens -- which are  
14 not heavily represented in the carcinogenic potency  
15 database -- could improve these models. And of  
16 course, one problem with this is that it will not be  
17 addressed by additional work -- is the variability and  
18 the imprecision and the extremely -- in the  
19 experimentally derived TD50s have already been  
20 discussed. And this, of course, stems from the wide  
21 variety of study design and performance aspects of the  
22 rodent cancer studies.

1                   So, the bottom line is, I think the  
2     answer is, yes, it is possible to get a general  
3     prediction of carcinogenic potency. How useful these  
4     numbers might be, remains to be determined. And just  
5     as Dr. Cronin predicted, the vast majority of the  
6     TD50s of the nitrosamines in the database, are, sort  
7     of, overwhelming the information from the less potent  
8     and the very, very potent carcinogens. So, we really  
9     need, unfortunately, to have a better spread of higher  
10    TD50 -- or lower potency carcinogens to look at to  
11    correctly model these chemicals. We do not have that  
12    in this case. And that is something that we are going  
13    to have to -- need to try to do some additional work,  
14    I think, to try to compensate for that aspect of the  
15    database.

16                   So, that would be my comment.

17                   DR. ATRAKCHI: Thank you.

18                   Dr. Eisenbrand? Dr. Eisenbrand, I  
19    think you are muted.

20                   DR. EISENBRAND: Sorry about that. I  
21    was quite impressed with the contributions until now.  
22    And I was very interested in. I may throw in some

1 further aspects that may be considered.

2 As far as I understand, this  
3 read-across validation exercise is going to find out  
4 ways to get reliable information about potency,  
5 including the extremes -- the very highly potent, and  
6 the non-potent -- or even, not ineffective. And that  
7 would be a little bit -- my point I would like to  
8 make, what about using our present day information we  
9 have about the non-carcinogenic nitroso compounds?  
10 And then, ask mechanistically minded, what makes them  
11 non-potent -- what makes them ineffective? And one  
12 can easily see that there is, of course, several  
13 layers of answers to that. Or maybe -- potency or the  
14 interaction with the nucleotides in the DNA. But  
15 there is, of course, a lot of metabolic action going  
16 on. And there we have activating, and disactivating  
17 metabolism. And I think mechanistically, it would be  
18 very important to input this information in.

19 For instance, we have -- of course, a  
20 very trivial molecular modifications -- the alpha C  
21 branching and the tert-butyl group. If that is  
22 attached, then the compound is not active, at all,

1 because there is no -- if there is alpha C  
2 hydroxylation on the other side, which may be a methyl  
3 group, then there is a split off, and the tert-butyl  
4 compound is not an affective -- agent. So, that is  
5 very easy, actually.

6 But what about, for instance  
7 isometrically substituted nitroso compounds. We had a  
8 series of investigations, for instance for n-methyl  
9 nitroso pyridines being either positioned --  
10 substituted in two, three, and four positions. So,  
11 there is all three isomers have been subbed. And if I  
12 were to ask the specialists which one they would  
13 predict to be carcinogenic, I would be interested to  
14 hear. But -- so, just to make it short, it is just a  
15 two compound that is the two isomer. And the full  
16 nitro is a group attached to the two position of the  
17 pyridine that is carcinogenic and mutagenic, where as  
18 the three and the four are not. And they are -- the  
19 answer is, again, there is an equilibrium between  
20 activating and disactivating metabolism.

21 And this not only true for this -- for  
22 these compounds, but also -- for instance, the example

1 I showed yesterday, which was cimetidine, which was  
2 mutagenic in the hamsters. But turned out to be  
3 non-carcinogenic in vivo in the rat. Again, because  
4 of disactivating metabolism.

5 So, I personally think it would be a  
6 good idea to use all the negative examples -- the  
7 examples of negativity we have and study why they are  
8 negative. And of course, as I said, they are trivial  
9 answers, but there are also answers that need to be  
10 really investigated in detail. So, I think that would  
11 be a enrichment of the whole procedure. That is for  
12 the preformed nitroso compounds.

13 My second suggestion would actually be,  
14 we need some system of -- some predictive system to  
15 get grips on the nitrosatability. How easy is a given  
16 compound -- maybe, of a new structure -- how easy is  
17 it nitrosatable? And I mentioned, yesterday, in my  
18 presentation, there is a richness in literature on  
19 that. Especially, Richard Loeppky has done a lot of  
20 work showing that there are specific structures that  
21 are very, very easily nitrosated -- tertiary amines --  
22 and I showed yesterday, also, the example of

1 motapizone and metamizole. The one easily splitting  
2 of -- very easily splitting of dimethyl nitrosamine.  
3 The other one forming in nitroso compound that is not  
4 carcinogenic.

5 So, I think this second point to study  
6 the nitrosatability, I think is important. It has been  
7 realized in the early times already. And that is why  
8 I mentioned the NIP test of the WHO, stemming from the  
9 early 80's -- which is a rugged test. But it very  
10 simply and chemically shows an information -- gives an  
11 information about the nitrosatability. I think that is  
12 something that pharma will need. A simple test -- if  
13 there is not a in silico prediction systems that are  
14 reliable enough, which I do not see at the moment --  
15 but there might be. And then, to use something like  
16 that.

17 Thank you.

18 DR. ATRAKCHI: Thank you,  
19 Dr. Eisenbrand. Very good points.

20 Dr. Hecht?

21 DR. HECHT: Yes. So, there are certain  
22 aspects of the structure and activity relationships of



1 nitroso compounds that we understand quite well, that  
2 have already been mentioned, just by Professor  
3 Eisenbrand, including alpha substitution. So, if you  
4 substitute the alpha positions, then you are going to  
5 inhibit the alpha hydroxylation metabolism. And  
6 probably decrease the carcinogenicity.

7 The other aspect is the polarity of the  
8 compound. So nitrosoproline is a great example. It  
9 is not metabolized. It is not carcinogenic. It is  
10 excreted unchanged. But there are other examples  
11 where if you substitute with a carboxy group, there is  
12 still activity maintained.

13 I am not optimistic that read-across  
14 and structure activity relationships are going to lead  
15 to predictability of nitrosamine carcinogenesis. Just  
16 look at the review by Kreuzman and Stewart, published  
17 in 1984. Look at the table in the back of over 200  
18 nitrosamines and their target tissues and activities  
19 and tell me whether predications can come up with  
20 these answers. I really doubt it. I am not  
21 optimistic, at all.

22 That is all I have to say.

1 DR. ATRAKCHI: Thank you, Dr. Hecht.

2 Dr. Kyrtopoulos?

3 DR. KYRTOPOULOS: I am afraid this is  
4 not really my field. And clearly, we are surrounded  
5 by great expert. So, I thank you, very much. I will  
6 pass on -- thank you.

7 DR. ATRAKCHI: Very good.

8 Dr. Zeiger?

9 DR. ZEIGER: Yes. Thank you. First of  
10 all, I appreciate -- definitely appreciated  
11 Dr. Cronin's introductory comments on this. It laid  
12 out the strengths and some of the weaknesses of the  
13 problems.

14 I look at this. There are a number of  
15 aspects to it. I remember Willie Lijinsky's early  
16 work in carcinogenicity, showing that relatively minor  
17 structural changes could lead to quite large  
18 difference and carcinogenic potency, and also, organ  
19 specificity. This is something that somehow would  
20 have to be worked into any QSAR or read-across system  
21 that we adopt.

22 Secondly, it has already been mentioned

1 by a number of people -- the high proportion -- the  
2 low proportion of negatives -- you know, in the  
3 database -- of clean true negatives in the database,  
4 makes it a problem. Otherwise, you are just stuck  
5 with -- without those negatives, you are just stuck  
6 with a possibility of a -- as was mentioned, a nitroso  
7 structure automatically gives you a conclusion of  
8 mutagenicity and carcinogenicity, which may not be all  
9 true.

10 And I am concerned -- you know, when I  
11 deal with QSAR systems -- of the quality of the  
12 literature that is used to train and develop those  
13 systems. And I have had the advantage of being able  
14 to work in the past with fairly pure -- you know, very  
15 pure nitrosamines synthesized by Lijinsky. But I have  
16 noticed that in the literature, there are -- outside  
17 of that, there are many of -- many potential problems.

18 One thing that just came to me when I  
19 was preparing for this symposium -- this talk, was  
20 that looking at -- for example nitrosodiethanolamine,  
21 which supposedly is a non-mutagenic nitrosamine. We  
22 tested it and published the data back a number of

1 years ago, that it was weakly positive in the Ames  
2 test. But then, looking further, I saw that the  
3 analyzed purity of our sample was only 78 percent.  
4 Would not take much of a potent nitrosamine, within  
5 that 22 percent impurity, to give us a positive  
6 result.

7 So, I think whatever data are used for  
8 any read-across, or QSAR, really has to be  
9 addressed -- the people who are using it have to  
10 address the quality of the studies -- or the purity of  
11 the nitrosamines. Because a small amount -- a small  
12 impurity of a potent nitrosamine will change all the  
13 in vitro reactivities of -- in vitro responses of a  
14 supposedly non-potent nitrosamine.

15 All that said, I think -- unless we  
16 want to do carcinogenicities -- you know, analyses --  
17 carcinogenicity studies on all potential nitrosamines,  
18 we have to develop our read-across and QSAR systems  
19 for this. Thank you.

20 DR. ATRAKCHI: Thank you, Dr. Zeiger.  
21 Dr. Rice?

22 DR. RICE: Having never worked in this

1 area or attempted what appear to be very formidable  
2 challenges in developing the assessment prediction of  
3 activity for nitrosamines, and using structural  
4 similarities, I do not think I can add anymore to what  
5 has previously been said. But I would second  
6 Dr. Hecht's caution about the complexity of the  
7 available data for nitrosamines, and hope that future  
8 improvements in this direction will shine more light  
9 in what remains to be a challenging area for  
10 prediction.

11 I have nothing more to say. Thank you.

12 DR. ATRAKCHI: Thank you. I have some  
13 questions to bring up. But I would like to know if  
14 anyone else from the panelists would like to comment  
15 on this question?

16 Okay. So, Dr. Cronin, one of the  
17 questions presented is, read-across analysis can be  
18 very subjective. What methods can be used to more  
19 objectively identify the most relevant analogs for  
20 risk assessment of a data poor in nitrosamines?

21 DR. CRONIN: Well, that is the killer  
22 question for read-across. Thank you for whoever asked

1 that one. And there is no simple way of asking --  
2 answering that.

3 Just to point out, if you are  
4 unfamiliar with it, there is the so call read --  
5 European chemical agencies read-across assessment  
6 framework sets out a number of criteria in which to  
7 evaluate your read-across. And also, there is quite  
8 a -- well, several papers on understanding  
9 uncertainties in terms of read-across. We have  
10 co-authored something recently, and there is more  
11 historic work, for instance, from Proctor and Gamble  
12 and various other authors, as well.

13 I think what we need to think is, we  
14 are going to start with the chemical structure. So,  
15 we need to understand, firstly, what the difference is  
16 between the chemical structure in our target molecule,  
17 where we have few data, or no data, an a-source  
18 molecule. If you understand the differences in  
19 chemical structure, the question you are actually  
20 asking, therefore, is -- are the differences in  
21 chemical structure significant enough that you cannot  
22 perform read-across? So, are the differences in

1 chemical structure going to change the toxicological  
2 profile, both in terms of toxicodynamic -- which is  
3 what we have been talking about mainly. But also,  
4 toxicokinetic, which is, sort of, the lost child of  
5 read-across in many ways. And we have not done a very  
6 good job, up until now, doing that.

7           So, we certainly have been looking at  
8 different approaches to doing that. One can do that  
9 in terms of just understanding the chemical  
10 structures, themselves. Do they have the same -- most  
11 fundamentally, the same functional groups. Is the  
12 arrangement around, the n-nitrosamine -- which we have  
13 heard is so important -- is that the same. If it is  
14 not, is that going to affect reactivity. And gaining  
15 that knowledge.

16           And then, also with any changes -- for  
17 instance with chain lengths -- if we have a basic  
18 analog that may be varying just in terms of a chain  
19 length, how will they affect bioavailability and  
20 toxicokinetic? So -- and we can also add into the  
21 mix, things like chemical similarity and so forth.

22           So, at some point, you need to make a

1 decision. At some point, you need to be able to say  
2 that the differences are not sufficiently significant  
3 to be able to not to read-across. And you may also  
4 need to go and take some measurements. Now, these  
5 could be in vitro measurements, they may be further  
6 calculations -- but to support your arguments to  
7 perform that.

8                   And one thing I would just like to put  
9 in your mind -- and I do not -- it may come up later,  
10 is the process of problem formulation. We have been  
11 thinking about just jumping in with QSAR and  
12 read-across. And we have not really been thinking  
13 about, well, how are we going to use that. And what I  
14 would recommend is that, if the agencies are going to  
15 use read-across, then they stand back and think, okay,  
16 what is the problem we are trying to solve here with  
17 read-across. So, it could be, very rapid screening  
18 and prioritization. It could be a much more detailed  
19 risk assessment. And there are different criteria for  
20 acceptance of those points. And your levels of  
21 uncertainty will be -- acceptable uncertainty would be  
22 different. So, put that in the back of your mind and



1 have some pre-defined criteria. And at some point,  
2 you have got to assess the situation you are with  
3 read-across and your analog and say, does I meet -- do  
4 we have sufficient confidence to be able to do this.  
5 If not, why don't we, and how would we get more  
6 confidence.

7 So, there is no easy answer. It is a  
8 process of intelligently using read-across in many  
9 ways. Thank you.

10 DR. ATRAKCHI: Thank you. The other  
11 questions is, is there enough data on higher molecular  
12 weight nitrosamines -- for example, more than 350  
13 deltons -- to assess the mutagenicity, carcinogenicity  
14 or un-tested nitrosamines in this size range?

15 DR. CRONIN: Well, I will start off by  
16 answering that very simple, that I do not know. But  
17 we have access to the data. And that would be quite a  
18 straight forward question to answer. But I cannot  
19 answer it definitively, yes, or no. You would have to  
20 go through the data resources.

21 And, again, as I said, with the problem  
22 formulation -- before you ask -- before you go and

1     interrogate the data, what do you mean by sufficient  
2     data? I mean, that is quite an interesting and  
3     leading statement to start off with. So, have some  
4     ideas about what your expectations would be, and what  
5     the answers would be that you would want to answer  
6     them.

7                     Thank you.

8                     DR. ATRAKCHI: Very good. Both  
9     positive and negative examples of mutagens,  
10    carcinogens are needed in order to develop a QSAR  
11    model. Are the available negative data sufficiently  
12    robust for this purpose? That is, were the examples  
13    tested at high enough concentrations?

14                    DR. CRONIN: I am going to answer the  
15    first part, in terms of QSAR methodology, and then,  
16    defer the second part, in terms of experimental  
17    design, maybe, to the experimental toxicologist.

18                    So, one thing I meant to say, and I  
19    forgot to say, in my description of QSAR is, we can  
20    have two types of QSARs. One is a categoric approach,  
21    where we might just predict activity. So, whether a  
22    substance is mutagenic, or not. And this is really

1 what we are referring to, here.

2 The second kind of QSAR is more what I  
3 was eluding to in my initial comments, which was that  
4 we were -- we are modeling at potency. Which we can  
5 do, as well, in theory, with mutagenicity. And there  
6 are some QSAR for mutagenic potency. At which time,  
7 we would not include the negative data.

8 So, I would just put those points in  
9 your mind. But certainly, we do need high quality  
10 negative data that we are certain of to develop  
11 models.

12 And I would -- I will pass it over to  
13 the experimental toxicologist to answer. Thank you.

14 DR. ATRAKCHI: Thank you. Anyone would  
15 like to take that part of the question?

16 DR. BUCHER: So, this is John Bucher.  
17 I -- you know, it has been stated earlier that greater  
18 than 90 percent of the studied nitrosamines are  
19 positive for carcinogenicity. And this is a -- this  
20 represents a huge problem with respect to the balance  
21 of positive and negative data that you need to create  
22 decent models.

1                   So -- and the other problem, of course,  
2                   is that the simple nitroso entity, in and of itself,  
3                   derives so much of the bioactivity, that you really  
4                   need to have strong confidence and extensive data to  
5                   be able to have the R groups on that nitroso be  
6                   determinative, and override this --

7                   DR. ATRAKCHI: Dr. Bucher, we lost your  
8                   audio. Dr. Bucher? Maybe, check your mute button,  
9                   again. Okay. Maybe, we will get back to Dr. Bucher  
10                  when he finds out -- hopefully, resolves the issue.

11                  Next question is, are there areas of  
12                  nitrosamine chemical space for which we have too  
13                  little data to make a QSAR predications?

14                  DR. CRONIN: That is a really good  
15                  question. And how to define nitrosamine chemical  
16                  space is the first question in this. And I guess,  
17                  what we -- if this was a more general question in more  
18                  general areas of chemistry, I would say, okay, tell me  
19                  all the structures that you have which contain a  
20                  nitrosamine, or the particular class of nitrosamine,  
21                  or what you are interested in, and think about your  
22                  domain. Which structures are in that domain. And

1 then, I would map on the data to that.

2 So, I would admit -- and I have just  
3 been simply looking at substances for which there are  
4 data. And what you would need to do to answer that  
5 question is go and find -- or consider all structures  
6 that would contain a nitrosamine group.

7 I mean, one way you can start doing  
8 that is just -- as I said, I went to OECD QSAR tool  
9 box, which is one tool of many. It is really  
10 downloadable. You could draw out all of the nitroso  
11 compounds in that. You could do the same in the US  
12 EPA dashboard or go to ChEMBL or PubChem. And do a  
13 search for nitrosamine compounds. And then, just map  
14 on the data for that, and see where you have good  
15 coverage, and where you are lacking coverage.

16 And you need to think what your  
17 criteria are for coverage. Do you just mean in terms  
18 of the structure that is the basis for reactivity? Or  
19 are you looking at all kinds of physical chemical  
20 properties.

21 So, I do not know the answer to that  
22 question. I suspect there will be areas where we are

1 quite data rich and got quite a lot of  
2 data -- probably do not need to do much more  
3 testing -- and areas where there will be distinct  
4 lacks of data.

5 Thank you.

6 DR. ATRAKCHI: Thank you. Another  
7 question is, it has been mentioned that the stability  
8 of the reactive intermediates -- or intermediate  
9 should be considered when predicting nitrosamine  
10 potency. Such calculations can be computationally  
11 intensive for complex molecules. How can this  
12 information be practically incorporated into a model  
13 for mainstream use?

14 DR. CRONIN: Again, really good  
15 question. And the -- what is great about that  
16 question is, it is implying the mechanistic  
17 interpretability of it. And there is no easy answer  
18 to that. If you got complex molecules and it is going  
19 to take a couple of weeks to do a calculation --  
20 potentially, it could do -- then, that is the reality.

21 The problem, of course, is, if you have  
22 a relatively large data set -- even 10 or 20

1 compounds -- then you could be in -- it could take  
2 quite a long time to create a model. The only way  
3 around that is to try and use parameters that may be  
4 less computationally expensive. I mean, I refer to  
5 quantum chemical parameters as you go down the areas  
6 in -- back into some empirical calculations -- you may  
7 be able to get results that are as good, or even use  
8 very trivial 2-D structure based type approaches. But,  
9 again, they just do not capture the subtleties of the  
10 activities cliffs or at all give out specific reaction  
11 mechanisms.

12                   There is no easy answer to that. If  
13 you get a high quality model that is based around a  
14 metabolic route -- or a reactivity route, and you got  
15 a good basis for that in calculation -- going down the  
16 levels of calculation does not -- it will make it  
17 cheaper and quicker, but it does not make it better or  
18 as good. Thank you.

19                   DR. ATRAKCHI: And we will take one  
20 more question. The -- in reference to Dr. Cronin's  
21 comment about challenges with justifying read-across  
22 assessments, any thoughts on what could be cheap and

1 rapid data to supplement and support read-across?  
2 Anything other than Ames test? Something that could  
3 provide quantitative data that could be correlated to  
4 LD50 values in an absolute or relative sense, versus a  
5 compound with a well-established TD50?

6 DR. CRONIN: I am a bit caught out by  
7 the LD50 comment. And I am probably taking that out  
8 of context. We have done a little bit of work with  
9 cytotoxic data, and there may be some benefit in that.

10 As I said, in read-across, we are  
11 building up knowledge and using NAM data. And in  
12 other areas of read-across, we have certainly been  
13 pulling in data from ToxCast and the high content  
14 data, metabolism data, and also, in silico  
15 predictions.

16 But what -- I think that is a great  
17 question, and I will pass it over to the experimental  
18 toxicologist and see if they can answer it -- so, in  
19 terms of are there rapid quick win types of in vitro  
20 or other assays that can support our read-across  
21 argument.

22 DR. ATRAKCHI: Thank you. Anyone from



1 the panelist would like to take this?

2 DR. BUCHER: This is John Bucher. And  
3 I must apologize. My computer -- I dropped the signal  
4 last time, right after I stopped talking. So, if you  
5 asked me a question, I apologize for not answering.

6 With respect to a follow up, there,  
7 I -- the only thing I can think of is, there are a  
8 number of in silico models for metabolism and for --  
9 you know, rapidity of excretion, and things of that  
10 nature, that might be useful to incorporate as second  
11 level steps, I guess.

12 DR. ATRAKCHI: Thank you, Dr. Bucher.  
13 Any other comments?

14 Okay. It is 11:02. We will take a 10  
15 minute break, and we will be returning 11:10, or  
16 11:12. Thank you.

17 (off the record)

18 DR. ATRAKCHI: I think we should go  
19 back and -- before we begin with question seven, there  
20 are a couple more questions on question six.

21 The first question is, there is a  
22 difference between QSAR and SAR, but they are being

1 used somewhat interchangeable. SAR is an approach  
2 that has been shown to be health protective when  
3 suitable analogs are identified. If nitrosamines with  
4 existing data can be mapped to major groups than a  
5 nitrosamine with limited data could be mapped to the  
6 appropriate classification based on structure. The  
7 scientific community would greatly benefit if a group  
8 of experts could help map the structural space of  
9 nitrosamines and associated supportable limit. Can  
10 this be done?

11 DR. CRONIN: I will start on that. I  
12 agree with the statement -- I am reading it, now. I  
13 certainly agree with that. I think the term, SAR, in  
14 the question, is -- to what I was talk about with  
15 read-across. And this is actually quite similar  
16 to -- I spoke a little bit about -- there is an ad hoc  
17 group being led by Lhasa Limited and LeadScope, and  
18 that has a number of industry and academic members. I  
19 am not part of that, I should add at this point. I  
20 have just been reviewing their work. So, that is  
21 part, at least, of what they have been trying to  
22 do -- is identify these groups in terms of structural

1 alerts that are associated with reactivity that we can  
2 understand the reactivity. And also, seeing within  
3 those groups, there seems to be some variations of  
4 potency, which are unsoundable and predictable. And  
5 that is quite all right, because what you would be  
6 saying is for a new molecule, you would be putting it  
7 into that structural group, and then, seeing where it  
8 lies in read-across terms. That might just be called  
9 a trend analysis, or even a small QSAR.

10 But I agree with the sentiment. And  
11 yes, I believe as long as we have got rational ways of  
12 grouping molecules, that is achievable.

13 DR. ATRAKCHI: Thank you. The next  
14 question is, along with the QSAR assessment, can we  
15 consider metabolism assessment of complex nitrosamine  
16 impurities, which would account to the bioactivation  
17 of nitrosamine into reactive diazonium ion that result  
18 in carcinogenicity? For example, if a compound gets  
19 converted into diazonium ion easily, it would be more  
20 potent?

21 DR. CRONIN: There is a couple of  
22 different aspects to this. Again, I am reading the

1 question. There is a couple of different aspects that  
2 would -- I would highlight.

3 If we are dealing with complex  
4 nitrosamine impurities, I am assuming -- I am not sure  
5 what that means, off the top of my head. So, I will  
6 give two opinions. It could be a complex structure --  
7 a large structure with much complexity in it. Or, it  
8 could be a number of different impurities in that way.

9 So, yes. It is possible to trade  
10 models for bioactivation. Some of the discussion  
11 before the break was around that. And indeed, they  
12 might be quite some hefty models, if they are going to  
13 be used computationally. But we should be able to  
14 calculate conversion into the reactive diazonium ion.  
15 What, of course, we need, there, is some kind of -- is  
16 some benchmark against -- so we need some data. We  
17 cannot, necessarily, just create a model de novo,  
18 without data to base the model on and understand the  
19 model.

20 So, my question -- if you were to come  
21 to me with that question, I would say, well, do we  
22 have data on which to base the model in the first

1 place. And I do not know the answer to that, off the  
2 top of my head. So, in other words, for  
3 nitrosamine -- I am sorry -- diazonium ion conversion.  
4 I suspect there probably are some kinds of data that  
5 we can use.

6 The second part to the question, if  
7 compound get easily converted, would it be more  
8 potent? I assume so. But I am not a particular  
9 expert in that area, and I would pass that over to  
10 other toxicologists to answer.

11 DR. ATRAKCHI: Thank you. Anyone would  
12 like to answer the -- that part of the question?

13 Okay. The other question is, should  
14 SAR/read-across focus on carcinogenicity endpoint, or  
15 consider separately the mutagenicity metabolic  
16 activation calculation by activated nitrosamine, or  
17 repair of alkylated DNA?

18 DR. CRONIN: That is a really great  
19 question, and I like that question a lot. It shows a  
20 lot of insight into what we are trying to do.

21 The history of read-across -- or  
22 probably the last decade of history of the

1 read-across, particularly in Europe has been to  
2 cope -- or to provide information for REACH endpoints,  
3 most specifically. So, in terms of the REACH  
4 legislation -- and again, I am just saying these  
5 comments from memory -- what we are trying to do -- or  
6 what we are assuming is that our read-across would  
7 be -- or have the same level of scientific competence  
8 that the animal test on which it is replacing would  
9 have.

10 The other implication, in terms of  
11 using read-across and in silico methods for REACH type  
12 endpoints is, that they should be relevant -- or they  
13 should be replicating the actually regulatory end  
14 point. So, that is why there is read-across attempted  
15 for carcinogenicity. And to me, these very complex  
16 toxicological affects are the most challenging to try  
17 to attempt read-across.

18 You go back to your same arguments that  
19 we had before about what level -- for a complex  
20 endpoint, what level of reliability and confidence can  
21 you have on that, on the basis of your understanding  
22 of the similarity and dissimilarity between two or

1 more compounds. And, it may be that we can never get  
2 there definitively for carcinogenicity, and we do need  
3 to add in other test data, as we were discussing  
4 before.

5                   However, the -- when we -- and I hate  
6 to use the word simplify -- but, when we are looking  
7 at slightly less complex endpoints, such as  
8 mutagenicity metabolic activation and alkylation, and  
9 so forth, then we are cutting down the possibilities  
10 for differences between molecules -- because clearly,  
11 here, if we are talking, certainly, about in vitro  
12 data, then we are eliminating a lot of the  
13 variability, in terms of toxicokinetic, and those  
14 issues -- and focusing in particularly on -- in API  
15 terminology, the molecular initiating event, and  
16 whether or read-across argument holds up in terms of  
17 the molecular initiating event.

18                   So, yes. We can apply SAR and  
19 read-across to all of those. I would say we can apply  
20 it to all of the endpoints and effects that are listed  
21 by the questioner. And it may be, then, you need to  
22 think, well, how are you going to use that

1 information.

2 So, if you get a good read-across, you  
3 can do a good read-across. For instance, for  
4 alkylation -- well, how does that relate to your  
5 ultimate safety assessment and risk assessment? So,  
6 that becomes a different question.

7 So, to answer the question, yes. We  
8 can do read-across. But I would also caution how are  
9 you going to use that information.

10 Thank you.

11 DR. ATRAKCHI: Thank you, very much.

12 Anymore comments on this question from  
13 anyone?

14 Okay. We can move to question seven,  
15 which is the last question. And it is focused on  
16 pharmaceutical manufacturing.

17 Question seven; Nitrosamines can be  
18 formed during manufacturing of the Active  
19 Pharmaceutical Ingredient, and/or the drug product.  
20 What are possible approaches to consider in order to  
21 reduce nitrosamine formation during manufacturing?  
22 Can nitrosamines be eliminated completely from the API



1 and/or the drug product?

2                   We heard from this -- yesterday, from  
3 Dr. King, on the evolution of the contamination  
4 incidents with -- of medicines with nitrosamines. Is  
5 it possible to eliminate nitrosamines from drugs, and  
6 particularly, in the final drug product, which is the  
7 entity will be taken by the patient? We know  
8 nitrosamines could form during various stages of drug  
9 manufacturing process. They could form during  
10 storage, during packaging. What are the parameters,  
11 or steps that could be followed to either prevent  
12 their formation, or reduce their amount to minimum,  
13 and maintain safe medicines?

14                   I will be asking my colleagues from the  
15 FDA to present on this -- or to answer this  
16 question -- to present on the challenges that we have  
17 with regard to manufacturing and the elimination or  
18 the minimization of nitrosamines.

19                   Dr. Keire?

20                   DR. KEIRE: Thank you, Aisar.

21                   So -- I mean, in the simplest terms --  
22 you know, any step in the manufacturing process of a

1 drug substance -- or drug product that leads to the  
2 conjunction -- the bringing together of a reactive  
3 amine -- a secondary or tertiary amine and a  
4 nitride -- or nitrous acid, can lead to nitrisation  
5 chemistry, and the formation of nitrosamines. So,  
6 that is the simple part, right?

7 And then, if you think about the range  
8 of different drug products and the complex chemistries  
9 that go into making them -- you know, then suddenly --  
10 you know, that gets a little more complicated. But I  
11 would say, that -- you know, it is not a nullable.  
12 All these difference processes can be examined with  
13 this nitrosamine lens, right? You know, looking for  
14 back -- what -- you know, steps that bring these  
15 factors together. And you know, one of the control  
16 aspects would be to -- you know, change that process,  
17 so that you are not bringing those two components  
18 together, if it is possible.

19 You know, another approach is to think  
20 about that process where -- you know, maybe there is a  
21 step -- an unavoidable step in the synthesis of a  
22 particular active pharmaceutical ingredient, that --

1     you have that step early in the process, and then, you  
2     provide subsequent purging capacity with other steps  
3     in the process before you get to the purified API,  
4     that remove nitrosamines. And of course, that has to  
5     be established -- you know, either through  
6     measurements or other ways of knowing that you are --  
7     you know, reducing or eliminating the nitrosamines  
8     from the process.

9                     So -- but I guess I do want to make a  
10    point -- is that -- you know, in some of the initial  
11    findings in drugs of nitrosamines -- you know, they  
12    actually had nothing to do with the drug itself,  
13    right? That -- you know, in one particular example,  
14    DMF -- dimethylformamide, is a solvent, in which the  
15    reaction was carried out in. And that was heated for  
16    a long period of time, near the boiling point of that  
17    solvent. And, of course, it is known that when you do  
18    that you get the formation of dimethylamine from DMF.  
19    And then, in subsequent steps in the process, there  
20    was a quenching reaction, which involved nitride.

21                    And so, what you had is a side reaction  
22    of a side reaction leaving to the -- leading to the

1 formation of NDMA. So -- you know, that is, kind of,  
2 a -- the example of one part of the complexity, right?

3 And then, the other part is that we  
4 have been surprised with -- is supply chain, right?  
5 There were certain manufacturers that were using  
6 recovered solvents, and they were -- the solvents were  
7 recovered in a way that led to their contamination by  
8 nitrosamines. So that when they were used in the  
9 synthetic process, where there was no risk of  
10 nitrosamines, they were present because they were in  
11 the recovered solvent used.

12 And then, the third, kind of, major  
13 consideration I the stability of the drug as  
14 formulated. So, there have been a couple of examples  
15 where the amount of nitrosamine increased over time,  
16 ranitidine is an example of that. And that is a  
17 degradant of the API.

18 So -- you know, all these things have  
19 to be considered in the manufacturer and the  
20 formulation, and the testing, right? You have to --  
21 you know, if there is risk, you have to test and you  
22 have to see if your process has purge capability, and

1 you have to know your supply chain is clean. But you  
2 know, if you have all those things going, it is  
3 entirely possible that you could eliminate nitrosamine  
4 contamination from the drug.

5 I mean, there may be cases where you  
6 may not be able to completely eliminate it, but you  
7 can certainly assume over the shelf life of the  
8 drug -- you know, in real world condition, that the  
9 drug is stable, so that the amount of nitrosamines  
10 does not go above an acceptable amount. And in that  
11 case, it would be safe for patient use.

12 So, I will stop there.

13 DR. ATRAKCHI: Thank you.

14 Dr. Johnson?

15 DR. JOHNSON: So, hi. Yeah. This is  
16 actually a really good question, and it is one that I  
17 think regulatory agencies and manufacturers have been  
18 struggling with for the last two years. I have been  
19 involved with the agency on the nitrosamine task force  
20 for about two years.

21 Some of the things that, I guess, we  
22 have learned since the very beginning, when we first

1 saw these, it was -- you know, in the sartans, and as  
2 Dr. Keire had mentioned, they were really, kind of,  
3 surprises. They were side reactions. And as we have  
4 gone on over the last two years, we have seen them pop  
5 up in a lot of different places, and our understanding  
6 of, kind of, how this happening, I guess, has  
7 expanded.

8 I do not think we still truly have a --  
9 you know, a complete understanding of all the possible  
10 ways. But from just the perspective of what I have  
11 seen as a chemistry assessor and being on this task  
12 force -- some of the things that I have noticed  
13 that -- directly related to the question, now -- what  
14 can a company do to help -- you know, minimize the  
15 formation of these -- or could they be eliminated  
16 completely.

17 So, some of what I have learned over  
18 the last two years is that in order to get a  
19 nitrosamine, you have got to have precursors. So, you  
20 need a secondary -- or tertiary mean, and you have got  
21 to have a nitrous aiding agent. And I think the one  
22 we have most commonly seen is nitrous acid. But there

1 are some others that could potentially be there. And  
2 the tricky part we found is -- as Dr. Keire alluded  
3 to -- a lot of times this is happening completely  
4 unrelated to the chemistry that is involved in  
5 actually making the API molecule. These are side  
6 reactions that are happening, kind of, unnoticed. And  
7 so that makes -- you know, a control strategy -- or  
8 understanding it difficult sometimes.

9                   So, I guess, some of the main  
10 places -- and just, kind of, reiterate what Dr. Keire  
11 said -- some of the main places we have seen where  
12 nitrosamine formation is occurring and things that you  
13 can do are, one, when you have got a synthetic scheme,  
14 where you have got both the nitrous aiding agent, and  
15 an anime -- so that could be amines there that are --  
16 aren't as -- anime bases -- tertiary anime bases --  
17 they could be secondary amines -- they could be a  
18 tertiary or secondary anime functionality on a  
19 starting material, or an intermediate. So, they are  
20 in the same synthetic process. So, the worst case  
21 scenario is when they happen to be in the same step.

22                   So -- I mean, the easiest way to

1 prevent this would just be to eliminate one of those.  
2 So, if you eliminate one of the agents -- one of the  
3 precursors, then, theoretically your risk of  
4 nitrosamines should -- you know, go away. But that is  
5 not always possible. It is not always possible just  
6 to eliminate these. There is some chemistry that just  
7 -- you know, requires a nitrous aiding agent, or  
8 requires anime bases. And sometimes it is just  
9 unavoidable.

10 So, if you have a case where they have  
11 to be used together, and you cannot -- you know  
12 eliminate one of them, it would be great if you could  
13 potentially not use them in the same step. If that is  
14 not possible, then -- you know, if the anime  
15 functionality is all on a starting material, or  
16 intermediate, you might consider -- you know, a  
17 protecting group on there. But, being aware that even  
18 if you have small amount of an unprotected anime, it  
19 is going to still react. So, you still -- if the risk  
20 is there, you have to think about what is going to  
21 form. And then, you have to have a strategy of  
22 determining whether or not it did not. If it did, to



1     what extent.

2                     If you could -- if the risk is that  
3     there is a nitrous aiding agent in one step, and the  
4     anime in several steps later, one thing that we found  
5     was industry was being surprised quite frequently they  
6     were getting nitrosamines, but if you looked in the  
7     synthetic scheme, they were not actually in the same  
8     step. They were actually separated by multiple steps.  
9     And there were actually -- you know, several workups  
10    in between. And what we discovered was that things  
11    travel through your process a lot farther than you  
12    think.

13                    And so, what I tell industry when I am  
14    talking to them, is you have to think holistically.  
15    You have got to look at the whole process. You have  
16    to think about what is in there, and you have got to  
17    understand how it is traveling through your process.  
18    So, even if they are not in the same step, they could  
19    potentially be traveling through and interacting more  
20    than you think.

21                    So, the other thing that we were  
22    surprised on in this -- discussed in the sartans case,

1 the -- there was nitrous acid that was deliberated  
2 added -- it was actually nothing to do with the  
3 chemistry. It was actually a cleanup step, because  
4 they -- there had been a reagent that was using that  
5 was needed to be destroyed. Nitrous acid was just  
6 there to basically destroy that reagent.  
7 Unfortunately, they had also used some tertiary anime  
8 bases.

9 And so, a lot of companies -- you know,  
10 they were able to use that outside the process,  
11 because it was just a waste management step. And so  
12 that was simple. And we all thought, well, that is  
13 great. They have removed one of the precursors.  
14 Things should be great. And yet, they were still  
15 seeing some nitrosamine formation. Obviously, much  
16 less. But it was still there. And after further  
17 investigation, it turns out that one of the reagents,  
18 sodium azide, has a considerable amount of sodium  
19 nitride in it. So, while they thought their process  
20 was nitrate free, it actually was brining in quite a  
21 bit.

22 And so, that is another tricky part --

1 is you got to understand where these nitrous aiding  
2 agents -- or amines might be getting into your process  
3 as impurities. So, again, a wholistic thinking. What  
4 exactly is coming into your process? What is in it?

5 In the case where these are coming in  
6 as impurities, a lot of times people were able just to  
7 put -- you know, a limit on that reagent for that  
8 particular impurity, and they were able to show that  
9 when controlled at these levels, nitrosamines were not  
10 really a big issue.

11 Another one that we have seen a couple  
12 of times -- and again, nitrous acid is the -- probably  
13 the most common nitrous aiding agent we have seen. We  
14 have also seen some nitrosamines forming because some  
15 APIs had some residual amines in them, and then, they  
16 were put through a fluid bed drier. And this is a  
17 known issue with the malting process. You know, if  
18 there is nitrous oxides in the air in the malting  
19 process, they know they can get nitrosamines. Well,  
20 the same things with a fluid bed drier. On a couple  
21 of occasions, we have seen -- where there were some  
22 residual amines in the API, and then, what was put

1 through the fluid bed drying process, they actually  
2 were picking up nitrosamines.

3 So, again, it is a -- kind of, an  
4 exercise in thinking wholistically about the whole  
5 process. Not single steps, not just single reagents,  
6 but thinking about how the whole thing comes together,  
7 and how it all interacts.

8 Another place we picked up  
9 nitrosamines -- and sometimes they are actually  
10 intermediates -- or they are actually -- you know, on  
11 the starting shelf. So sometimes they are part of the  
12 process. And in that case, it is a little easier to  
13 control, because you know it is there. And then, it  
14 is just a matter of making sure that you have the  
15 control strategy that -- you know, controls those at  
16 an acceptable level.

17 And, as to the question, can we just  
18 eliminate them entirely, that is our hope. For the  
19 last two years, that is what we have been hoping -- is  
20 can we just eliminate them entirely. And in some  
21 cases, yes. They have been, by eliminating the  
22 precursors. Sometimes people have added just extra

1 purification steps, and they have been able to get  
2 those levels down to where they are either  
3 undetectable, or below a level that we are concerned.

4 But these are good questions. They are  
5 ones we are still dealing with. They are ones we are  
6 still learning about. And the longer we go, the more  
7 we learn.

8 But, anyway, that is what I have to  
9 share. So, thank you.

10 DR. ATRAKCHI: Thank you, very much,  
11 Dr. Johnson.

12 Dr. Dorsam?

13 DR. DORSAM: Well, good morning, and  
14 thank you. So, this is a fantastic question. And the  
15 first part of the question regarding what are the  
16 possible approaches to consider in order to reduce  
17 nitrosamine formation, I do have to say that I look to  
18 Dr. Keire and Dr. Johnson for answers to that question  
19 frequently. And they have outlined many of the  
20 different routes of formation, as well as mitigating  
21 strategies in this response, but also in many other  
22 forums.

1                   Coming at this from a pharm/tox  
2 perspective, I would say that the two real key  
3 approaches -- I have two things that come to mind.  
4 Number one is awareness. And what Dr. Johnson said is  
5 that there is a need for a wholistic approach to one's  
6 drug product. That is a key element, because it is  
7 not one particular root cause. There are several  
8 potential contributors. And so, I think awareness  
9 that there are many potential places where  
10 nitrosamines might be forming in a product specific  
11 manner. That awareness is key to then, mitigate. And  
12 mitigate would then go towards -- you know, where is  
13 the root cause, and modifying the factors. So, I  
14 think, full awareness is a critical first piece. And  
15 then, mitigation, thereafter.

16                   And I focus a little bit more on the  
17 second part of the question. Can nitrosamines be  
18 eliminated completely from the API or drug product?  
19 And I think that in some cases the answer is, yes.  
20 Nitrosamines can be eliminated. Although, we have --  
21 eliminated is really not detected according to an  
22 assay that is appropriately sensitive. So, qualifying

1     it that way, we have seen that it can be eliminated  
2     from some drug products and APIs. I think it is  
3     accomplished through identifying the risk,  
4     understanding the chemistry, and then, making  
5     adjustments to reduce the risk of formation. And it  
6     is has been a credit to good science and good  
7     manufacturing -- good drug manufacturing, that we have  
8     been able to see nitrosamines can be eliminated in  
9     some cases.

10                     I focus a little bit more on some of  
11     those other cases that we are still working with right  
12     now. There are some drug products where mitigation  
13     presents more challenges. And in that case, then we  
14     are looking more heavily at that risk/benefit scenario  
15     for a particular drug and a particular population.

16                     In those cases where that mitigation is  
17     more complex, we are working in pharm/tox very closely  
18     with our chemistry colleagues, with our clinical  
19     colleagues, drug shortage staff, as well as compliance  
20     colleagues. In order to really understand the  
21     feasibility of reducing nitrosamines in these complex  
22     cases -- to understand the medical necessity of a drug

1 for a particular population. And then, not only the  
2 medical necessity, but what is the appropriate balance  
3 of risk from the impurity, and the benefit of that  
4 drug. So, this is something that is  
5 multi-disciplinary in nature. It is complex. It is  
6 very drug specific. And we engage in that sort of  
7 discussion on a case by case basis.

8 I think it remains to be seen whether  
9 some products can fully eliminate nitrosamines. But  
10 we are certainly going to continue on working in a  
11 multi-disciplinary fashion, and with international  
12 regulatory bodies, to really ensure that we are  
13 maintaining that right balance of safe drugs. Again,  
14 really trying to inform the risk, because I am coming  
15 at it more from a pharm/tox perspective.

16 So, whether they can be completely  
17 eliminated or not -- our focus is to inform the risk.  
18 And I think that we are looking to identify what is a  
19 one in one hundred thousand cancer risk for these  
20 drugs. We have heard about this over the last two  
21 days. We have posed some questions to the panel that  
22 we are grappling with on a frequent basis. We have



1 plenty of data to support that these are impurities  
2 that are potent carcinogens across many species. And  
3 we will continue to use all available data to identify  
4 what is the risk of a particular compound.

5 In cases where there is carcinogenicity  
6 information, we will use that data to inform what is a  
7 safe level for a drug. We will use data -- you know,  
8 in a surrogate approach to identify where there are  
9 imperfect carcinogenicity data. We are continually  
10 focused on how to appropriately characterize the risk  
11 and potency of compounds, and both for cases where  
12 there are plenty of data, as well as where there is  
13 none. So, we are going to do the best with all  
14 available information for those cases where  
15 nitrosamines cannot be eliminated.

16 So, we are focused on risk  
17 characterization. We will maintain a one a 100,000  
18 cancer risk threshold for these impurities in drug  
19 products. We will certainly take the advice of the  
20 panel into consideration, interact with our national  
21 regulators in order to continually move through how to  
22 grapple with these nitrosamines as a broad issue,

1 which impacts a bunch of the -- many different drugs.  
2 Because, ultimately, we are going to keep our focus on  
3 acceptable risk, in light of all the available  
4 information.

5 And so, with that, I think I have  
6 finished my comments, for now. And I will pass it  
7 back to Dr. Atrakchi.

8 DR. ATRAKCHI: Thank you, Dr. Dorsam.  
9 Dr. McGovern?

10 DR. MCGOVERN: Yes. Thank you. And  
11 good morning. I think the previous responding -- you  
12 know, really covered the issues well. You know, and  
13 again, coming from a safety perspective on this issue,  
14 and -- you know, and similar to Dr. Dorsam, really  
15 more focusing on the latter question of -- you know,  
16 can nitrosamines be eliminated. And I think as we  
17 have heard -- you know, with sufficient time and  
18 effort, yeah. Probably in most cases nitrosamines can  
19 be eliminated. And some of those cases that effort  
20 is -- or the required effort is going to be less than  
21 other cases, you are also dealing with issues such  
22 as -- you know, as we have talked about contaminations

1 in solvents, what water sources you are using -- you  
2 know, possible presence in excipients can be a  
3 complicating factor. And sometimes -- you know, it is  
4 unavoidable in order to be able to synthesis your API.  
5 And sometimes, as Dr. Johnson had mentioned, some  
6 changes that are made to try to avoid nitrosamine  
7 formation, may have unintended consequences that --  
8 you know, lead to issues.

9 And then, of course, as analytical  
10 techniques improve -- you know, where you once thought  
11 you did not have any nitrosamines present, and the  
12 lower you look, the more likely you may be to find  
13 them at -- you know, very low levels. So, the  
14 question can really be -- you know, do they need to be  
15 completely eliminated in all cases in order to  
16 maintain patient safety? So that overall risk/benefit  
17 concept that Dr. Dorsam was -- you know, speaking to.

18 And at a certain point, the effort to  
19 eliminate nitrosamines may exceed the corresponding  
20 impact on patient safety. Given the multiple way in  
21 which people may be exposed to nitrosamines -- you  
22 know, we have talked about over the last day and a

1 half, or so -- you know, such as food, water,  
2 polypharmacy being another one -- it seems reasonable  
3 that drug sponsors implement appropriate quality be  
4 design -- or GMP approaches in order to -- you know,  
5 try to avoid the presence of -- or formation of  
6 nitrosamine impurities -- you know, as best they  
7 can -- and with due diligence, in terms of the supply  
8 chain, as well.

9                   However -- you know, as we have seen,  
10 these impurities may be difficult to control, or  
11 predict, even, in certain circumstances. So -- you  
12 know, we need to balance the efforts required to  
13 control impurities versus the overall impact they  
14 would have on patient safety, so that we are  
15 not -- you know, over expending resources  
16 unnecessarily on this particular issue, when they  
17 could be better used elsewhere, in terms of -- you  
18 know, the public health issues involved with drug  
19 development.

20                   As Dr. Dorsam mentioned -- you know, we  
21 have identified acceptable intake levels for various  
22 impurities, to date. More will likely be generated in

1 the future. And we have done a lot of work in this  
2 area in conjunction with regulatory partners around  
3 the world. In general, if a sponsor has demonstrated  
4 a reasonable effort to avoid or control these  
5 impurities, and the impurities are controlled within  
6 the AI limits as indicated in -- you know, our  
7 guidance and other regulatory guidance documents --  
8 that level of control -- you know, certainly seems to  
9 be reasonable.

10 We have had -- you know, discussion  
11 over the last day and a half -- also taking into  
12 consideration -- you know, TD50 approaches, versus  
13 benchmark dosing. We can consider to take a look at  
14 that, and consider -- you know, those differences, and  
15 what impact they may have on -- in terms of acceptable  
16 levels. As well as -- you know, assessment in  
17 conjunction with -- you know, dietary intake levels,  
18 and endogenous production. And certainly, we have  
19 talked about -- you know, what data gaps may be  
20 present in those cases.

21 So, I think -- but you know, certainly  
22 is a start, those -- if you know, impurities are

1 controlled within those AI limits, that seems to be --  
2 certainly, be a relatively safe level of control to  
3 being with. But certainly -- you know, if steps can  
4 be taken to completely avoid the presence of the  
5 nitrosamines, I think that is better for everybody.  
6 But as we all know, that is not always possible.

7 So, thanks.

8 DR. ATRAKCHI: Thank you, Dr. McGovern.

9 Dr. Hecht?

10 DR. HECHT: Yes. I think the key  
11 factor that was mentioned earlier is awareness. And  
12 if we have awareness of the possibility of nitrosamine  
13 formation, I think in most cases it can be mitigated.  
14 I think the sartan example is a good one -- where  
15 there was not sufficient awareness that when using  
16 sodium nitride to destroy the excess azid that was  
17 used to make the triazole in the -- that is in the  
18 drug, that -- you know, nobody thought about the fact  
19 that nitride can lead to nitrosamines by reacting with  
20 a small amount of impurity in the solvent. So, I  
21 think, now, we have awareness of this possibility,  
22 which should lead, presumable, to much less of a

1 problem.

2 I suppose there is some cases where,  
3 perhaps, the formation of nitrosamines cannot be  
4 avoided, due to the particular procedures that are  
5 used in the drug manufacturing process. In that case,  
6 might have to take other approaches, such as improved  
7 purification methods. But we have the tools to detect  
8 nitrosamine impurities. And very well, that whole --  
9 and presumably, at this point, we should have the  
10 awareness to avoid their formation.

11 Thank you.

12 DR. ATRAKCHI: Thank you, very much.

13 Dr. Adamson?

14 DR. ADAMSON: Yes. Thank you. I would  
15 agree with the previous commentors. And I would say  
16 that it basically involves good manufacturing  
17 processes and practices. And good manufacturing  
18 practices include quality management, sanitation and  
19 hygiene, building and facilities, the equipment that  
20 is being used, the raw materials, the personnel -- and  
21 that includes awareness -- the validation and the  
22 qualification of the people that are manufacturing.

1                   And it has been mentioned by Dr. Dorsam  
2   and echoed by Dr. Hecht, but complete awareness. So,  
3   look at the chemical reaction that is taking place.  
4   Look at the method of synthesis. Look at the  
5   reagents. Look at the solvents. Is there nitride in  
6   the solvents? If you are using water, look at the  
7   nitride level. And as been mentioned, avoid solvent  
8   dimethylformamide, which -- if possible. Certainly,  
9   avoid dimethylamine, if possible. And you can --  
10   necessary, if you are recovering the solvents for  
11   efficiency, effective recovered solvents. And I  
12   cannot emphasize enough, check the contaminated  
13   equipment. That needs to be check, is all.

14                  And then, also, avoid processes as has  
15   been stated, involving secondary and tertiary means,  
16   particular with nitride and other acid conditions.  
17   And then, also, check all batches -- and add a medium  
18   batches, if possible. And check the status of the --  
19   not only the API, but of the finished product, and  
20   check it under adverse conditions, such as excess of  
21   heat and moisture. And I think if you do this, you  
22   will have checked most of the boxes that are necessary



1 in order to avoid nitrosamine formation.

2 Can it be eliminated completely from  
3 API and the drug product? That certainly is the goal,  
4 but I am not sure in some cases if it is necessary.  
5 And then, as previously said, you need to look at the  
6 amount, and -- that is present, and you need to look  
7 at the risk/benefit of the drug that is being used.

8 So, those are the comments that I would  
9 say.

10 DR. ATRAKCHI: Thank you, Dr. Adamson.

11 Any other comments from anyone else on  
12 the panel?

13 DR. EISENBRAND: Yeah. This is --  
14 Eisenbrand speaking. I totally agree with what has  
15 been said. And I also agree that I think the driving  
16 principal behind mitigation is awareness. And that is  
17 what my colleague, Dr. Hecht, has already lined out.

18 It is extremely important to be aware  
19 of all possibilities. One example that has been  
20 mentioned by Dr. Johnson was that in a drying process,  
21 the air that is being used is not purified, but it is  
22 just environmental air containing nitrogen oxides.

1 And then, we get in a problem you may not have been  
2 aware of before.

3 But there are also some very straight  
4 forward things. For instance, the drug diclofenac has  
5 normally been formulated as a sodium, or a potassium  
6 salt. But in some instances, I do not exactly know  
7 for what reasons, it has been used and marketed as a  
8 dimethyl or a dialkylamine salt. So, that needs to be  
9 checked whether this is really necessary, or it is  
10 just probably a me too approach.

11 So, there are several of these things  
12 that can be used. But there are other totally  
13 unexpected sources of potential contamination. And  
14 one maybe also the use of nitrocellulose in packaging  
15 or printing, because it has been found out earlier,  
16 already, that nitrocellulose is a very strong  
17 nitrosating agent. We came across that because it was  
18 found in Europe that -- in cosmetics, the nail  
19 lacquers are very often formulated with  
20 nitrocellulose. And of course, they contain  
21 nitrosamines if they are secondary amines. Yeah.

22 So, there are expected and unexpected

1 things. And it is awareness of costs that is driving  
2 this mitigation. But one has to be open, also, to  
3 potentially unexpected things to scrutinize and  
4 mitigate nitroso compound formation during manufacture  
5 up to formulation and packaging.

6 Thank you. That is my --

7 DR. ATRAKCHI: Thank you. Any other  
8 comments?

9 Okay. There are some questions from  
10 the attendees. One of them is, as part of the  
11 nitrosamine risk assessment exercise, pharma companies  
12 are reaching out to the manufacturer of excipients  
13 asking for presence of potential nitrosamines in their  
14 excipients. Are these -- are there available data on  
15 levels of nitrosamines in excipients? Surely GMP  
16 process for APIs should guarantee absence of potential  
17 formation of nitrosamines, but the same should be  
18 applied to excipients that are much higher in quantity  
19 in the drug product. I am interested in the opinion  
20 of the experts on this.

21 Who would like to start?

22 DR. KEIRE: I guess, I can comment a

1 little bit. I think that -- you know, the main  
2 concern with the excipients is actually the presence  
3 of nitride. I do not think we have had any reports of  
4 excipients containing nitrosamines. Although, again,  
5 if the excipient -- particular excipient contains a  
6 secondary amine, and also nitride is present, then it  
7 is a possibility.

8 But the main concern I think that we  
9 have had, is that there is nitride present in these  
10 excipients -- or other amines that could be oxidized  
11 by some means to nitride. And then, that could lead  
12 to some chemistry with the API when it is formulated.

13 I do not know if Deborah, or others  
14 want to add to that.

15 DR. EISENBRAND: Could I ask a  
16 question? Is the excipient -- is that filling  
17 material? Or what is it? I mean, is it mainly  
18 starch, or is it inorganic material? Could you just  
19 explain a bit? I mean --

20 DR. KEIRE: Yeah. I mean -- yeah.  
21 There are many, many different excipients. You know,  
22 cellulose binders, magnesium stearate, coatings -- you

1 know, that are -- but for the most part they are not  
2 amines -- they do not contain amine. So, they -- you  
3 know, as you said, starch, cellulose based binders,  
4 that --

5 DR. EISENBRAND: Oh. Okay.

6 DR. KEIRE: -- those are the major  
7 components. But others should feel free to weigh in  
8 as well.

9 DR. EISENBRAND: I ask this because, we  
10 came across years ago that some -- certain inorganic  
11 materials -- for instance like bentonites or --  
12 contain nitrogen oxides. So, they appear to be -- as  
13 we found at that time, as a source for artifactual  
14 nitrosamine formation. They can nitrosate amines.  
15 And maybe, they can also nitrosate drugs. So, I think  
16 it is important to know that is not the nitrosamine  
17 content, per se, that may be relevant. But it is the  
18 nitrosating possibility -- those things.

19 DR. KEIRE: Yeah. And I think that has  
20 been our -- you know, our major concern -- focus --  
21 you know, question that we have been trying to ask.

22 You know, I guess I should say that

1     there is still a lot unknown, here, right? You know,  
2     we are really -- you know, working with the  
3     manufacturers and they are doing root cause analyses,  
4     we are trying to do -- you know, get better  
5     understanding about what is present in these  
6     excipients. And you know, in terms of these, kind of,  
7     other process related impurities in the excipients  
8     themselves, and how that could lead to chemistry in  
9     the solid state -- in the tablet -- you know, where --  
10    or in the process of formulation.

11                 So, it is a -- there is a -- still a  
12    lot of unknown in this area. We are still learning.

13                 DR. ATRAKCHI: Thank you. The next  
14    question is, if nitrosamines are eliminated mostly  
15    from the API and/or the drug product, will there be  
16    any way to determine whether nitrosamines will form as  
17    the drug product sits on a shelf or in the person's  
18    body?

19                 DR. KEIRE: Well, I guess I can speak  
20    to the first part of that. I mean, the -- you know,  
21    the drugs are put on stability testing, right? So, in  
22    that, there are, kind of, standard conditions for

1 that -- you know, 40 degree C, 75 percent humidity, is  
2 an example of an accelerated stability condition. And  
3 that -- or they are -- you know, put in -- they are  
4 just stored at room temperature, at the temperature  
5 that they are going to be -- you know, distributed in,  
6 in some supply chain. And for the period of time,  
7 over the shelf life of the drug, and -- you know, they  
8 would be tested periodically, if there was a risk for  
9 nitrosamine formation. And so, with that data -- you  
10 know, the agency could say, yeah, this is a -- we --  
11 you know, we would approve this drug for this period  
12 of time -- you know, to be on the market, right? They  
13 would have an expiration date on it -- you know,  
14 established with those data.

15 DR. ATRAKCHI: Thank you. Any other  
16 comments?

17 DR. JOHNSON: Yeah. This is Deborah.  
18 Yeah.

19 And so, there is another thing -- you  
20 know, it -- when something goes on stability -- you  
21 know, your analytical methods are good for what you  
22 are looking for. So, some of the problem, these are

1 forming in drug products. And you know, if people are  
2 not looking for them, and they are really low in  
3 level, and they miss them.

4 But another place you might pick this  
5 up is during product development, where you were doing  
6 your drug excipient compatibility studies. Especially  
7 with -- you know, excipients that are known to have  
8 nitrite contaminants. That is another place that you  
9 could be looking to make sure that -- you know, you  
10 are not picking up nitrosamine formation, there. And  
11 you may have to explore several vendors, because --  
12 you know, not every vendor is equal, they may not have  
13 the same process in making the excipient. So, that is  
14 just another place that you could be looking in --  
15 again, in a proactive manner -- a wholistic manner,  
16 to -- you know, you are, kind of, building the quality  
17 into the product. Is -- you know, up front, is there  
18 a potential for this API -- especially if it has got a  
19 secondary or tertiary amine functionality, or you have  
20 residual.

21 You know, a lot of times some of these  
22 amines carry over because -- you know, they were used



1 in the process. If you got residual amines in the  
2 process -- you know, are there some excipients that  
3 are known to have these nitrite -- you know,  
4 contaminants -- you know, do some work up front to  
5 ensure that you are -- you know, kind of, picking  
6 things up early.

7 DR. ATRAKCHI: Thank you. Any other  
8 comment on this question?

9 Okay. The next question is, is it  
10 possible that nitrosamine impurities in drug products  
11 will keep on increasing during the shelf life of the  
12 drug product? What if some impurity is below the  
13 limit of detection, or tolerable levels, at the time  
14 of packaging, and it increased above the tolerable  
15 levels after six or 12 months, when it is reached to  
16 the consumer? How can you assure stability after a  
17 drug is in the marketplace?

18 DR. KEIRE: Yeah. I think I, kind of,  
19 answered this question earlier. I mean, the -- you  
20 know, the -- we have to be given data that says that  
21 the drug is sufficiently stable, such that -- you  
22 know, it -- talking about nitrosamines -- that, that

1     nitrosamine limits succeed in specified limit over the  
2     shelf life of the drug. There has to be data that  
3     would show that before the drug was allowed on the  
4     market. So --

5                     DR. ATRAKCHI: Okay.

6                     DR. KEIRE: Oh. And I guess -- sorry.  
7     The other point there is detectible. You know, it  
8     would not be detectible at the initial state, but then  
9     it would be detectible later, right? And that goes --  
10    that speaks to the point of appropriate analytical  
11    methods to detect the presence, or the absence of  
12    something.

13                    So -- and that is a -- you know, we --  
14    you know, the FDA and also, actually, international  
15    regulatory partners have, kind of, established limits  
16    in guidance documents that say what they would call  
17    appropriate, right? I mean, one of those is, kind of,  
18    a 30 part per billion bar that has been set. I mean,  
19    of course, that might be difficult with a drug that  
20    is -- analytically, that might be difficult with a  
21    drug that has a very high dose. But for most drugs,  
22    that is going to be quite a load limit. And so that

1 is the approach that is being taken for -- you know,  
2 defining appropriately -- appropriate detection limits  
3 to say something is absent.

4 DR. ADAMSON: Yeah. I think the  
5 manufacturers might also want to consider the  
6 possibility of adding an anti-oxidant to the drug  
7 finished product.

8 DR. ATRAKCHI: Thank you.

9 Next question is, can stoichiometric  
10 ratios between amine or nitride levels be used as a  
11 rational to exclude a nitrosamine formation in drug  
12 product, considering that sometimes amines and  
13 nitrides may be concurrently present in negligible  
14 amounts in associated to unfavorable conditions for  
15 nitrosamine formation?

16 DR. KEIRE: Well, yeah. That is a bit  
17 of a complicated question. I think it depends on  
18 the -- yeah. It depends very much on circumstance.  
19 You know, I -- you know, you do need certain ratios to  
20 get some chemistry to go, right? So, you know, it --  
21 certain amounts of nitride and amine may be necessary  
22 to get significant reactions under -- you know, a

1 particular condition. So, it is a little bit  
2 difficult to answer that question, because of the --  
3 we need -- kind of, need a specific case to talk  
4 about, there.

5 DR. EISENBRAND: Could I comment, just  
6 for a second, on this?

7 I think it is worthwhile for the  
8 manufacturers if they are facing such a question of  
9 stability -- the one thing, I think, is very clear, if  
10 it is only very small, tiny traces of nitrosatable  
11 compounds, then, I think it is obvious that there is  
12 no risk. But one should also consider under -- you  
13 know, if make a false condition storage testing --  
14 storage stability testing, one should think of having  
15 such a condition where you have environmental and NOx  
16 concentrations. Because, we have found out -- and  
17 many others, later, also -- that there is an  
18 interaction between solid material that contains  
19 nitrosatable and NOx, of course. And you can get  
20 them -- the question of stability, then, needs to be  
21 widened by this consideration. That it may be that  
22 the drug is sitting in a car -- or sitting somewhere

1 else -- or you have it in a bar, where it is smoking,  
2 and this sort of thing. And then, you have the  
3 exposure to NOx. And maybe, you can solve the whole  
4 thing by using the right packaging, or course. But  
5 one should look at this.

6 DR. KEIRE: Yeah. I mean, I think  
7 there is a big focus on -- you know, real world  
8 conditions, right? You know, the hot mailbox, the  
9 glovebox in the car -- you know, the human bathroom.  
10 You know, I mean, if you think about those things --  
11 you know, what does it experience in the truck in the  
12 middle of summer in the southern U.S., right? You  
13 know, so -- you know, before it gets to the shelf.

14 So, you know, I mean, you cannot  
15 completely model all those conditions. But you know,  
16 you try to get appropriate data that can be predictive  
17 of stability under a variety of conditions. And you  
18 know -- and those are -- you know, have been, kind of,  
19 internationally harmonized in ICH documents, about --  
20 you know, which conditions are standard conditions  
21 that can be used to establish stability.

22 DR. ATRAKCHI: The next question is, is

1     there any information regarding azocolorants and/or  
2     colorants with amine groups? Also, colorants normally  
3     have a non-negligible quantity of unspecified  
4     impurities.

5                     DR. KEIRE: Yeah. I mean -- you know,  
6     I -- if the colorant contains -- you know,  
7     diethylamino group, or a secondary amine that might be  
8     reactive -- you know, that -- you need to look at it  
9     through that awareness lens, that we have been talking  
10    about, as a potential source of nitrosamine.

11                    I mean, generally, the colorants are  
12    there in very small amounts. But you know, again, it  
13    is a case by case, kind of awareness question. And an  
14    understanding of what is going into the drug. But --

15                    DR. ATRAKCHI: Thank you. Is good risk  
16    assessment enough? When should testing for  
17    nitrosamines be triggered?

18                    DR. JOHNSON: So, I will give a crack  
19    at that. So, if you look at the FDA nitrosamine  
20    guidance, it has several steps. And the first one is  
21    to do the risk assessment. And it clearly says that  
22    if -- when you do the risk assessment, if you do

1 detect a risk, then you should do confirmatory  
2 testing. So, that is confirmatory testing.

3 So, if you do the confirmatory testing,  
4 and you use appropriate sensitive methods, with  
5 appropriate limits of quantitation in detection, and  
6 you do not detect these nitrosamines, then, you have  
7 confirmed that, yes, it was a risk that -- you know,  
8 your process has mitigated it, and -- you know, the  
9 product does not appear to be at risk for  
10 nitrosamines.

11 But if you do the confirmatory testing,  
12 and you are actually detecting these above the limit  
13 of quantitation, then, clearly, your process is  
14 creating them. And then, you have to move into the  
15 realm of the control strategy. And you have many  
16 control strategies open to you. And one of those  
17 might be -- you know, testing -- you know, putting a  
18 limit and a test forward in a starting material or  
19 intermediate -- something upstream. Or, you always  
20 have the -- you know, the option of testing the API.

21 So, there is some different ideas of  
22 testing. There is the confirmatory testing that has

1 to be done when you have identified a risk in your  
2 risk assessment, that does not necessarily -- you  
3 know, result in -- you know, normal -- you know,  
4 routine testing in the API.

5 DR. EISENBRAND: Dr. Atrakchi, may I  
6 have one further addition -- information to the former  
7 question about the azo dyes?

8 DR. ATRAKCHI: Yes, please

9 DR. EISENBRAND: Yeah. The Scientific  
10 Committee on Consumer Safety of the European  
11 Commission in 2012, I think it was, issued two  
12 opinions about nitrosamines in cosmetics. And the  
13 first one dealt with azo dye constituents of  
14 cosmetics, and -- the risks -- so this is publicly  
15 available information to that. Thanks.

16 DR. ATRAKCHI: Thank you. Considering  
17 the surprise, in quotes, nature of materials carrying  
18 through more steps than we through, or from coming in  
19 with other materials, do we think we need to start  
20 testing API routinely?

21 DR. JOHNSON: I will answer that one,  
22 if I can.



1                   So, our goal with the nitrosamine  
2 guidance was never intended to tell people they have  
3 to test every single batch of API all of the time.  
4 You know, that is, kind of, the quality by testing.  
5 And I think we are encouraging people to have quality  
6 by design -- to build quality into the process.

7                   And so, I think what we have learned  
8 throughout this process is, there was just some  
9 assumptions that materials were being removed from a  
10 step during the workout. That -- you know, nitrites  
11 in some of these that they were water soluble -- they  
12 were being removed. And I think what we learned was  
13 they are not being removed as thoroughly as one  
14 thought.

15                  So, again, being wholistic -- realizing  
16 that potentially there are these materials -- you  
17 know, precursors in the process, then if you  
18 understand how they are being purged, then -- you  
19 know, final API testing is not necessarily -- you  
20 know, you do not have to do that. You might just have  
21 a in process control to make sure your nitrite level  
22 is below a certain level, or an amine level is below a

1 level. You might know that -- you know, there is  
2 potential for a particular nitrosamine forming in an  
3 intermediate step. And again, that could be  
4 controlled upstream, using an option three approach --  
5 you know, as an API -- or as an IPC, or an  
6 intermediate specification.

7 So, there was never any -- you know,  
8 expectation that people would have to test everything.  
9 What we just learned was that things in the process  
10 were carrying through more steps than people thought,  
11 and that you cannot assume. I guess, that was the  
12 bottom line that we learned. Just do not assume. You  
13 have to understand the process and the purging  
14 capability completely, and then, move from there.

15 DR. ATRAKCHI: Thank you. Does every  
16 nitrosamine demand equal levels of removal or  
17 avoidance?

18 DR. KEIRE: Well, I think I will hand  
19 that to my pharm tox colleagues to -- I think -- you  
20 know, they have established limits that, kind of,  
21 point to the -- I mean -- you know, NDMA is at 96  
22 nanograms as the AI limit, versus NDEA being at 26.5.

1 So, there is distinction between those two. And, as  
2 well as others. So -- but, I will leave that to my  
3 pharm toxicologist to weigh in.

4 DR. MCGOVERN: This is Tim. I can jump  
5 in. I -- currently, the identified limits we have in  
6 place range from 26 to about 96 nanograms per day.  
7 So -- you know, given the uncertainty in all these  
8 calculations, you can argue there is really there is  
9 not a lot of difference in that at those levels.

10 So -- you know, there is some  
11 differentiation in the approach taken. Of course,  
12 those are not every nitrosamine. Those are NDMA, and  
13 NDEA are probably the two with the most robust  
14 databases. There may be some others out there, as  
15 well. Certainly, if we are dealing with a nitrosamine  
16 that has yet to be identified, where we identify a  
17 significantly higher acceptable intake. Then, yeah,  
18 you could -- you know, obviously, you would treat  
19 those somewhat differently than you would with the  
20 current ones we are dealing with.

21 DR. DORSAM: That is right. I  
22 emphasize that. To say that we have tried to be

1 mindful about each chemical -- each compound as it  
2 comes in, to identify what is the risk associated with  
3 that compound. And so, I think, if -- you know, not  
4 all nitrosamines are created equal, and there are --  
5 you know, some that are more potent, some that are  
6 less potent.

7 We do know that there is need for care  
8 with this class of compounds. And so, we will use  
9 whatever data are available to assess the risk for a  
10 particular compound, realizing that the risk for this  
11 compound may be different than NDEA, or NDMA. You  
12 know, we are trying to go mindfully compound specific  
13 for each of the products that we are encountering a  
14 nitrosamine issue. And I think that we will continue  
15 to do that.

16 DR. MCGOVERN: And as Dr. Dorsam  
17 mentioned earlier, you would also -- can take into  
18 consideration -- you know, what the drug product is,  
19 what the proved indication is for, and potential  
20 impact on drug shortages -- you know, especially for  
21 severe disease indications.

22 DR. ATRAKCHI: Thank you. I do not see

1 any more questions. Does anybody else notice other  
2 questions that maybe we can answer at this time?

3 DR. ZEIGER: This is Errol Zeiger. I  
4 have one quick question -- or comment. And it is  
5 based on my lack of knowledge about manufacturing  
6 logistics. But it can always -- one possible take  
7 away from all these discussions is that every  
8 manufacturer really needs to have an analytical  
9 laboratory to support them. And are there good -- are  
10 there analytical methods that they would have to  
11 obtain -- have to use, because -- you know, at the  
12 levels of nitrosamines that are being measured, one  
13 cannot use just any analytical method, but essentially  
14 what FDA would consider the state of the art effort.  
15 So, is this going to be a requirement -- you know, for  
16 manufacturers?

17 DR. KEIRE: Right. I mean, I think  
18 they have to have the technology, and the appropriate  
19 analytical tools to make the measurement -- you know,  
20 that is fit for this purpose, right? And which is  
21 down in the part per billion -- you know, part through  
22 million range. So, this is trace analysis that does

1     require instrumentation.

2                     And you know, we -- you know, the FDA  
3     has provided, I think, to date, publicly posted on the  
4     website 11 different methods. And certainly, the  
5     European OMCL have also provided methods -- made them  
6     publicly available on really a wide variety of  
7     platforms. I mean, the -- you know, many of the FDA  
8     methods -- you know, we, kind of, transitioned over  
9     time from using GCMS approaches to LCMS -- high  
10    resolution LCMS approaches, because we had that  
11    equipment available, number one, and it was best and  
12    most sensitive that we had.

13                    And I think, every manufacturer -- you  
14    know, has the access to these kinds of labs, or they  
15    have contact research organization where they have  
16    testing done. And that is the expectation. You know,  
17    the first thing you need to do is to have this  
18    analytical target for what you need to measure. You  
19    know, pharm tox provides us with that underpinning  
20    of -- you know, you need to control this particular  
21    impurity at this level. You know, whatever it is --  
22    96 nanograms. And then -- you know, with that

1 information, the analytical chemist is developing  
2 methods that are appropriate for that.

3 But -- so, I think there is actually a  
4 pretty wide range of technology that is available. I  
5 do not think that this a real limiter for most  
6 pharmaceutical manufacturing firms. So, the  
7 technology is there. The methods are available --  
8 publicly available. So -- you know, and that is --  
9 you know, one of the things -- the reason we do that  
10 is to, kind of, speed this process. We -- you know,  
11 if there is a question if there is a risk, we want  
12 them to make measurements and give us the data so that  
13 we can be assured that their product is of appropriate  
14 quality.

15 And -- oh. And I guess, one other  
16 thing. I want to -- I guess, often times there are  
17 too much focus on the ATI, and the synthesis. I  
18 think -- you know, we do want to emphasize that the  
19 drug product -- you know, and the formulation of that  
20 drug product really needs to be considered, as well,  
21 because we have cases where the API has no  
22 nitrosamines, but then, when it is made into a

1 formulated product, then nitrosamines appear. So,  
2 this is not only on the API manufacturer side. It is  
3 also in the drug product manufacturing side.

4 I will stop there. Thank you.

5 DR. ATRAKCHI: Thank you, Dr. Keire.  
6 One more question. Is -- can the panelists comment on  
7 the formation of API related nitroso impurities? What  
8 factors contribute to these impurity's formation? Is  
9 this a common occurrence across all products? And  
10 this is a -- the nitroso group is attached to the API,  
11 itself.

12 DR. KEIRE: Right. You know, I think  
13 if you look at the structures of --

14 DR. EISENBRAND: Ranitidine.

15 DR. KEIRE: -- many -- yeah.  
16 Ranitidine. Yeah. If you look at the structures of  
17 many of the drug substances, they have secondary  
18 amines that have the potential to react and for  
19 nitroso drug substance related impurities. So, this  
20 is also a consideration.

21 And the same question needs to be asked  
22 about the drug substance -- the molecule itself,



1 whether it can -- has the potential to form a nitroso  
2 compound.

3 DR. ATRAKCHI: Would you say this is a  
4 common occurrence among -- the last part of the  
5 question -- is this a common occurrence across all  
6 products?

7 DR. JOHNSON: So, if I could make a  
8 comment. When you are looking at the potential of the  
9 actual API forming nitrosamine, I mean, you can really  
10 look at the structure. If you have an API molecule  
11 that has a secondary amine -- I mean, you have to  
12 consider that a nitroso -- you know, API -- you know,  
13 degradant might form, because you have got a secondary  
14 amine. Especially, if you got one where the alkyl  
15 groups are tied back, and the amines is -- you know,  
16 really, really out there.

17 The -- you know, if it has got a  
18 tertiary anime -- well, ranitidine had a tertiary  
19 anime in it. I would think just from an organic  
20 perspective that a secondary amine functionality is  
21 probably at more risk than a tertiary amine. But, if  
22 the molecules got those function -- those amine

1 functional groups on it, then you have to consider  
2 this, because some of the excipients may contain  
3 nitrous aiding agents. Or -- you know, if you are  
4 doing fluid bed drawing in the API or in the drug  
5 product, again -- you know, if there is NOx available,  
6 it is possible.

7 So, you can literally look at the API  
8 molecule and do a real quick risk assessment just  
9 based on the actual structure.

10 DR. ATRAKCHI: Thank you. So, I think  
11 to summarize the -- really, this question, it is  
12 awareness, and it is wholistic approach. To me, it is  
13 all about chemistry. And we have the state of the art  
14 tools in the 21st century, and very sophisticated  
15 techniques that could eliminate -- or, at least,  
16 extremely minimize the levels of nitrosamines in  
17 pharmaceuticals. And certainly, the evidence for the  
18 sophisticated techniques, at least in the late 90's  
19 and early 2000's, is the food manufacturing and  
20 processing. It has -- it is a success story that  
21 really led to extremely lowering the levels of  
22 nitrosamines in foods. And I believe this can be

1 achieved with drugs, as well.

2 We are close to 12:00 -- I am sorry.

3 Go ahead, Dr. Keire. Please.

4 DR. KEIRE: Well, I guess I just wanted  
5 to add to that. I think that is a really pertinent  
6 comment. I mean -- so, we are not the only  
7 industry -- you know, the pharmaceutical industry --  
8 that has had to manage this -- you know, not having  
9 nitrosamines present in the product. And I think --  
10 you know, that Dr. Eisenbrand has already -- you know,  
11 presented on the malt kilning step in beer. And you  
12 know, I was actually reading about this. And it used  
13 to be that -- you know, there was microgram per liter  
14 of nitrosamine -- NDMA present in beer because of this  
15 particular step. But then, when there was knowledge  
16 gained about this step and this process, then they  
17 ultimately eliminated that. And you know, more recent  
18 surveys of beer show almost no nitrosamines.

19 And so, I think -- you know, it just  
20 is -- you know, the food and beverage industry has  
21 gone through this transition the pharmaceutical  
22 industry is now facing this same task. But it is not

1     unachievable. Other have -- you know, succeeded in  
2     eliminating or minimizing the presence of these  
3     things. So, I remain hopeful that the pharmaceutical  
4     industry can be the same.

5                     DR. ATRAKCHI: Fully agree. Thank you,  
6     very much.

7                     It is almost 12:30. We will take the  
8     lunch break from 12:30 -- or from now, until one  
9     o'clock. And we will resume -- we have some other  
10    questions -- just follow up questions from yesterday,  
11    as well as today, that we can provide to the panelists  
12    to answer. And then, we can wrap up.

13                    Thank you, very much. Enjoy your  
14    lunch.

15                    (off the record)

16                    MS. PAINTER: Good afternoon, good  
17    evening. We are back. It is 1:01, here on the East  
18    coast.

19                    DR. ATRAKCHI: Welcome back for the  
20    last part of the second day and final day of this  
21    workshop. What I would like to do now, is we have  
22    some of the questions from the attendees, that

1 includes both from yesterday's discussion, as well as  
2 today. I would like to go over those. And that way  
3 we have a full discussion of everything that has  
4 been -- that is interesting and important to  
5 everybody.

6 The first question is, can you see a  
7 correlation between nitrosamines and radiation safety?  
8 Would the linear no threshold model for radiation  
9 safety be applicable for nitrosamines moving forward?  
10 Therefore, for drug manufacturer, we essentially have  
11 to eliminate the potentials for nitrosamines formation  
12 for a drug to be considered safe. Or, essentially,  
13 also, adopt the as low as reasonably applicable  
14 principal.

15 Who would like to start this  
16 discussion? Anyone?

17 DR. EISENBRAND: Maybe, I start?

18 DR. ATRAKCHI: Yes.

19 DR. EISENBRAND: I think there is a  
20 difference between radiation safety and the dose  
21 response towards nitrosamines. I would say for  
22 pharmacologic reasons, there should be somewhere in

1 the dose response curve of nitrosamines, a threshold  
2 where the dose is so low that no measurable -- let's  
3 say, DNA damage is to be seen. And if we agree that  
4 DNA damage is a very important point used as a  
5 biomarker for the potency as one may say -- yeah --  
6 reflecting to biological activity on the target DNA,  
7 then we -- I think, now adays, will have the means to  
8 find out such a dose level, where DNA damage is  
9 negligible -- in a sense that it is just diving in the  
10 background DNA damage we have anyway. And this is a  
11 possibility that definitely deserves research and  
12 investigation. And I think with today's instrumental  
13 analysis means, we can do that. We have done this,  
14 for instance, for acrylamide, where one easily can  
15 follow down the dose response down to a level where  
16 the ancillarisation, in that case dives into the  
17 background of -- into the biological background, more  
18 or less. So that is a difference to -- you know,  
19 radiation, in that sense.

20 DR. ATRAKCHI: Thank you,  
21 Dr. Eisenbrand.

22 Anyone else would like to comment on

1 this?

2 DR. EISENBRAND: Just perhaps, to add  
3 on it, that is why I think a no risk level would be  
4 the -- as low as reasonable achievable would be the  
5 way to go in this question.

6 DR. HECHT: I basically agree with  
7 this. But I also recall the conclusion of the -- of  
8 bio assay of dimethylnitrosamine and  
9 diethylnitrosamine by Peto, and Grasso, and others, in  
10 which they concluded there was no evidence of a  
11 threshold. So, I do not know that we have the data to  
12 really establish a no risk level for compounds like  
13 dimethyl and diethylnitrosamine, as an example.

14 DR. EISENBRAND: Mm-hmm. Yeah. I  
15 totally agree, Steve. I think, this would, perhaps,  
16 cover dose ranges that are below the manifestation of  
17 tumors. So, in other words, one could, perhaps,  
18 follow down by studying DNA alkylation to further down  
19 dose levels, until one reaches, perhaps, somewhere a  
20 level where it really is insignificant from the  
21 physiological background of DNA alkylation. That is  
22 what I mean, actually.

1 DR. HECHT: Right. Yeah. I agree.

2 DR. EISENBRAND: By the way,  
3 Dr. Atrakchi, when I -- there was also a question  
4 concerning the acceptable intake estimates -- the  
5 default acceptable intake estimate -- estimated some  
6 type of -- this alluded to the big difference between  
7 nitrosodimethylamine and nitrosodiethylamine. And  
8 actually, I think this shows the difficulty of relying  
9 on the TD50 when determining such estimates, because  
10 it would mean -- it would reflect a more than -- about  
11 a three times higher potency of diethylnitrosamine, as  
12 compared to dimethylnitrosamine, if you look into the  
13 pository of 96 nanogram per day for  
14 dimethylnitrosamine, versus 26.5 for methyltyrosine.

15 And that is why I favor, really, the  
16 BMDL 10 values, because if you look into the BMDL 10  
17 values, they reflect much better. The vicinity, so to  
18 speak, of the biological effects of dimethyl and  
19 diethylnitrosamine, of course, still showing that  
20 diethylnitrosamine is the more potent with BMDL value  
21 of 18 microgram per kilogram, versus the BMDL 10 of  
22 n-nitrosodimethylamine of 27. But it is a much



1 smaller difference as the one from the default  
2 acceptable intake estimates, based on the TD 50 --  
3 just as a general note of caution from my side.

4 DR. MCGOVERN: Dr. Eisenbrand, this is  
5 Tim McGovern. Just a follow up question regarding  
6 benchmark dosing approaching.

7 I think a good argument is made for  
8 using the entirety of the dose response curve as the  
9 benchmark dose uses. We get into some subjectivity  
10 and variability as -- you know, as you use that data,  
11 then, to support calculation of a PDE -- permissible  
12 daily exposure level. And the application of  
13 uncertainty factors -- and depending on what level of  
14 uncertainty factors you use across the various factors  
15 that are applied, you can end up in a wide range of  
16 permissible daily exposure levels.

17 And you know, often times -- you know,  
18 especially with nitrosamines, they can be -- even in a  
19 fairly conservative approach, you can up in an PDE  
20 that is -- you know, significantly -- you know, in  
21 least in order of magnitude greater than the AI  
22 calculation. Do you have any comments, or any of the

1 other panelists, in terms of -- you know, using that  
2 approach and the application of uncertainty factors,  
3 and differentiation or the difference in the PDE  
4 versus AI levels, that are the outcome of those  
5 calculations?

6 DR. EISENBRAND: Yeah. As I mentioned  
7 already, I think that unsafety or safety factors are  
8 default factors. Like, the AI values. And maybe the  
9 BMDL values are -- you know, considering the much more  
10 important portion of the dose response curve, as far,  
11 of course, as they are available. That is just the  
12 case for very few of the nitrosamines, like ethyl --  
13 diethyl and dimethylnitrosamine. And, you know, that  
14 is why I think these BMDL 10 values reflect better the  
15 potency differences, as the AI estimates derive to.

16 DR. ZEIGER: This is Errol Zeiger. I  
17 might say, just as an aside, the genetic toxicology  
18 community has been moving more and more towards the  
19 use of BMDL for in vivo comparisons. There are some  
20 recent publications by Ilsey -- I do not remember who  
21 the first authors were -- that show that the BMDL was  
22 much more stable and useful than LOEL, or other

1 measurements. And the group at Health Canada, led by  
2 Paul White, in Ottawa, has been looking at BMDLs as a  
3 very effective for comparing related chemicals, such  
4 as polycyclic aromatics in vivo. But also comparing  
5 responses in different tissues -- you know, from the  
6 same animal. So, hopefully, in the future, more and  
7 more gene tox data will be coming out as -- with BMDL  
8 calculations, instead of just LOEL, or just -- you  
9 know, maximum response calculations.

10 DR. EISENBRAND: No. I agree. EFSA --  
11 it -- the same, actually -- favoring the BMDL process.

12 DR. ATRAKCHI: So, in general, how  
13 would the results compare, that are available for the  
14 same compounds -- how do they compare between the BMDL  
15 and the TD 50? How far are they off? Or are they  
16 comparable?

17 DR. EISENBRAND: No. They -- the AI  
18 estimate reflect the TD 50 values in a way. You know,  
19 they are derived by exultating to one in a hundred  
20 thousand risk. And there is a big difference in the  
21 AI values between dimethyl and diethylnitrosamine, not  
22 reflecting the true biological difference and potency.

1 They are much closer. Of course,  
2 n-nitrosodiethylamine is more potent. But not by a  
3 factor of three.

4 DR. ATRAKCHI: But I also think the  
5 values -- the limits will go much higher for the --  
6 for -- maybe not -- I mean, maybe not all  
7 nitrosamines, but the NDMA and NDEA, if you use BMDL.  
8 They are probably going to be even not in the cohort  
9 of concern if you use the BMDL. And that is a fairly  
10 big jump from what is indicated in M7.

11 DR. EISENBRAND: No. The way out --  
12 and so for instance sabers, is that they say we do not  
13 take any acceptable intakes for these compounds -- for  
14 the cohort of concern compounds. We just calculate --  
15 or -- yeah -- derive the distance between the 10  
16 percent, or you may take a five percent BMDL, where  
17 you -- and the consumers exposure. And in a  
18 general -- a very general way, they say if the  
19 distance is more than 10,000, then there is no  
20 concern. Very -- as a -- over the sum --

21 Here, we are not totally at the 10,000.  
22 We are between -- I would say, 6,000 and 10,000. But

1       there is a big difference, still, between.

2                   DR. ATRAKCHI:   Right.   There was a  
3       question earlier this morning along these same lines  
4       for NDMA and NDEA.   The question is, can one of you  
5       address why NDMA is considered one of the most  
6       concerning nitrosamine impurities based on discussion  
7       during the day, day one, when it currently has an AI  
8       of 96 nanogram per day, versus NDEA and others that  
9       have a lower AI, at 26.5?   If NDMA is of a greater  
10      concern, why does not -- why it does not have a lower  
11      AI?

12                  DR. EISENBRAND:   Yeah.   That is what I  
13      have just addressed with my remark to the AI estimates  
14      and the BMDL 10 models that actually are, in that  
15      case, more realistic.

16                  DR. ATRAKCHI:   Right.   I just thought I  
17      should read the question from the attendees.   Thank  
18      you.

19                  The next --

20                  DR. MCGOVERN:   And this is Tim.   I  
21      think it --

22                  DR. ATRAKCHI:   Yes?

1 DR. MCGOVERN: -- might be safe to say  
2 that they are both highly potent. And you know, with  
3 these types of calculations, I would suggest there is  
4 not a big difference between 26 and 96 nanogram per  
5 day, in terms of potency, because there is a lot of  
6 uncertainty around those values to begin with.

7 And -- you know, I guess, in terms of  
8 endogenous levels, maybe more of the focus is on NDMA  
9 just because that has been the more commonly observed  
10 of the nitrosamines.

11 DR. EISENBRAND: Yeah. That is really  
12 fair. I think -- I agree, totally. But you know,  
13 this raises such questions. Let's see -- these  
14 estimates. I agree with you, that, that is not a big  
15 difference, actually.

16 DR. ATRAKCHI: Certainly, considering  
17 the dosimetry and the tumors that they both induce,  
18 fully agree that these numbers are not very meaningful  
19 between the two. They both are very potent mutagens  
20 and carcinogens.

21 The next question is, can panelists  
22 comment on the use of incorporating normal variation

1 in DNA repair gene expression in humans into risk  
2 assessment models? Anyone would like to comment?

3 DR. KYRTOPOULOS: Can I respond? This  
4 is Kyrtopoulos. Can you hear --

5 DR. ATRAKCHI: Yes, please.

6 DR. KYRTOPOULOS: Yeah.

7 DR. ATRAKCHI: Yes. We can hear you.  
8 Thank you.

9 DR. KYRTOPOULOS: Yeah. Okay. Well,  
10 first of all, first question is, which DNA repair  
11 genes we are speaking about. Among the nitrosamines,  
12 which are found in drugs. MGMT is one that we discuss  
13 a lot. And it is relevant to carcinogenesis by the  
14 methylating or, maybe, the ethylating agents, also.  
15 But we do not know it is all in connection with  
16 carcinogenesis by other longer chain nitrosamines,  
17 which are found as impurities in drugs.

18 It is quite probable that their  
19 pre-carcinogenic DNA damage is -- may well be repaired  
20 by other mechanism -- like, the excision repair  
21 mechanisms.

22 So, in contrast to MGMT, which is just

1 a single gene, excision repair involves multiple  
2 steps, multiple genes, and there, one has to start  
3 asking which genes to use are markers of repair  
4 efficiency.

5           The other, and probably more important  
6 issue in my -- problem, in my opinion, is that whereas  
7 in simple animal models we can see, clearly, the  
8 affects of DNA repair variation. Animals  
9 overexpressing MGMT, for instance, are resistant to  
10 NDMA carcinogenesis, and conversely MGMT knock outs  
11 are much more susceptible -- the -- in the case of  
12 carcinogenesis in man, in human populations, it is  
13 much more difficult to come up with relationships  
14 between the moderate -- I mean, the normal variation  
15 in DNA repair and a carcinogenic susceptibility.  
16 There are rare cases where there are, again -- there  
17 is genetic lack of some genes, which result in serious  
18 cancer susceptibility. But those are fairly extreme  
19 cases. Especially for -- I mean, in the case of  
20 smoking related cancers, there is some knowledge about  
21 the variation excision repair and its impact on  
22 susceptibility. But, if we speak about nitrosamines,



1 we cannot really point to a specific cancer which we  
2 believe is caused by nitrosamines, so as to be able to  
3 investigate in a quantitative way, the relationship  
4 between the variation in DNA repair and risk, so as  
5 being incorporated in risk assessment.

6 So, I am afraid this is just not  
7 possible. Thank you.

8 DR. ATRAKCHI: Thank you. No comment.  
9 I will go to the next question.

10 My understanding is that the use of  
11 linear extrapolation from TD 50 to one in 100,000 risk  
12 assumes that there is no impact of DNA repair on the  
13 dose response curve. If that is the case, why would  
14 the setting of less than lifetime limits be based on  
15 an understanding when repair is exceeded?

16 DR. BUCHER: Oh. If I -- maybe, I can  
17 take a stab at this one. I think those two are  
18 actually unrelated. I think that the issue of less  
19 than lifetime involving some concepts of where repair  
20 processes might be exceeded were in those situations  
21 where there was quite a large potential dose of  
22 nitrosamine given for a very short amount of time.

1 And in our -- in my discussions of this, and in our --  
2 what I think we were talking about, was given  
3 situations where nitrosamines might be present in  
4 drugs at the acceptable intake level, or not much  
5 higher for short periods of time -- that these kinds  
6 of concepts would not necessarily apply where DNA  
7 repair processes would be exceeded.

8 So that was the way I took that  
9 question.

10 DR. KYRTOPOULOS: Yes. May I follow up  
11 on that?

12 DR. ATRAKCHI: Yes, please.

13 DR. KYRTOPOULOS: Yes. In fact, I  
14 think I pointed out rather the opposite. That we are  
15 in the dose -- in the linear dose area of the dose  
16 response when we are speaking about exposure levels,  
17 which include exposure coming from the environment and  
18 endogenous sources, even if we are over estimating  
19 that kind of exposure. Plus, the exposure that would  
20 come from the drug if we had imposed the standard risk  
21 assessment level -- 10 to the minus five -- that was  
22 well within the linear area -- really, a part of the

1 dose response curve -- so that even if were to exceed  
2 that within certain limits, obviously -- but even if  
3 you were to exceed that, we would still be -- by  
4 applying the LTL approach, we would still be in the  
5 dose response -- in the linear part. And that is why  
6 I had said that from the point of your DNA damage,  
7 LTL -- application of the LTL approach would be  
8 permissible. The reservation I expressed was that we  
9 do not know the other factors which affect cancer  
10 risk -- other biological processes, like -- sorry --  
11 cell replication, DNA adduct formation -- how they  
12 respond to increase doses. But from the point of view  
13 of DNA adduct formation, we have -- suddenly, we are  
14 not suggesting by applying LTL we would be risking  
15 running into conditions of exhaustion of repair. No.

16 DR. ATRAKCHI: But the conclusion from  
17 what you said, Dr. Kyrtopoulos, is that with all these  
18 reservations and concerns you have, the conclusion is  
19 that it is not a good idea, because of these other  
20 unknowns that involved. It is not a matter of the  
21 exceeding the DNA adduct formation, but it these  
22 others --

1 DR. KYRTOPOULOS: Yeah.

2 DR. ATRAKCHI: -- factors that we do  
3 not know about. Therefore, the less than lifetime  
4 approach is not a good approach to use for  
5 nitrosamine. Is that correct?

6 DR. KYRTOPOULOS: Yes. Yes. That is  
7 right. I -- if for reasons of expedience one has to  
8 use it, it should be used with great cautions, because  
9 we do not know how these other biological factors,  
10 which are -- make important contributions to the  
11 overall cancer risk. Very -- and let's remember -- I  
12 mean, we saw some data, yesterday, focusing on the  
13 liver, coming from the rat studies. And the liver is  
14 the main target for -- of -- let's say  
15 dimethylnitrosamine in the rat, and also for -- both  
16 in terms of DNA adducts. And -- but also, in terms of  
17 carcinogenesis. But that need not be the -- so, in  
18 all species. In fact, for example, in the Pattes  
19 monkeys, which we have looked at, we see extensive DNA  
20 damage, extensive accumulation of O6 methylguanine in  
21 many of the tissues. So, if we extrapolate our  
22 discussions -- or, rather open up the framework of our

1 discussions to other tissues, we can see that we are  
2 introducing a lot of additional unknowns. How various  
3 biological processes in operate in different tissues.

4 So, we have too many unknowns. And  
5 this is why I said that one should take the decision  
6 to apply the LTL approach hesitantly. And if they --  
7 we do, it should be with great caution.

8 DR. ATRAKCHI: Thank you. That is much  
9 clearer, at least in my mind. But in that case -- so  
10 the O6 adduct formation as biomarkers, may not be --  
11 well, by itself -- on its own, is not appropriate. We  
12 have to incorporate many other parameters with a DNA  
13 adduct, in order to make it make sense. Does that --

14 DR. KYRTOPOULOS: Yes. Ideally, this  
15 is exactly as you describe it. In practice, of  
16 course, we often have to use -- we can only use a  
17 limited number of tools, which have certain -- satisfy  
18 certain characteristics. And we do tend to use DNA  
19 adducts -- especially, if there are others which are  
20 involved in -- on the biological pathway, like O6  
21 methylguanine does -- is mutagenic. So, it is thought  
22 that it is actually directly contributing to the

1 generation of the mutation in oncogenes, or whatever  
2 else, which eventually drive the carcinogenesis.

3 So, if we have the opportunity to use  
4 it -- and this single biomarker, yes, we should use  
5 it. But we should keep in mind the limitations in its  
6 use. Yeah.

7 DR. ATRAKCHI: Very good. Thank you.  
8 Anyone else would like to comment on this?

9 Okay. Next question is, so far it  
10 seems that we do not have assuring data for less than  
11 lifetime to be safe with higher nitrosamine levels,  
12 even with short duration exposure. Do we know  
13 thresholds for adduct formation -- or of DNA repair?

14 I think we probably answered that  
15 question.

16 DR. KYRTOPOULOS: Yes. I think so.  
17 And, in fact, I pointed out that we have no evidence  
18 as far as O6 methylguanine is concerned of any -- a  
19 threshold. If you -- I went into the literature  
20 today, actually, because I had seen this question.  
21 And I looked up some papers which claim that they see  
22 non-linearity in the dose response. It turns out that

1 every time you see this claim, it is because they used  
2 high doses, which were generating so much O6  
3 methylguanine that they were depleting the repair  
4 enzyme.

5 So, if we are speaking about exposures  
6 at the levels that we are speaking about -- these low  
7 levels, there is no good -- no evidence of a threshold  
8 for adduct accumulation.

9 DR. ZEIGER: Well, actually, there has  
10 been some shown of -- a group at University of Swansea  
11 led by George Johnson, looking at low levels of  
12 alkylating agent, was an inducible DNA repair enzyme.  
13 I do not remember which particular one, because I do  
14 not have the paper handy. But they did clearly see a  
15 threshold --

16 DR. KYRTOPOULOS: What -- yeah. I  
17 remember --

18 DR. ZEIRGER: -- of a mutation, and of  
19 an adduct formation -- or adduct persistence.

20 DR. KYRTOPOULOS: Was that an O6  
21 methylguanine adduct?

22 DR. ZIEGER: I think it may have been.

1 But I -- the paper came out a couple of years ago, and  
2 I just do not remember the details.

3 DR. KYRTOPOULOS: Yeah. Yeah. I do  
4 not remember the details. But anyway, other papers  
5 which I tried to look up today, it was clear that they  
6 were using doses which, in my opinion, were very  
7 likely to have been impacting on the methyltransferase  
8 levels.

9 DR. ZEIGER: Oh. Agreed. One of the  
10 major problems we face in the field is a lot of the  
11 experiments are done at the high dose -- in the high  
12 dose, subtoxic range, whereas we are trying to  
13 extrapolate -- or draw conclusions from low dose  
14 administration, as we would see with nitrosamines.

15 DR. KYRTOPOULOS: Yeah.

16 DR. ZEIGER: And we know that once we  
17 get to the high dose, we are often not in a linear  
18 relationship. But we have to somehow draw a straight  
19 line down to zero to do the risk assessment for low  
20 doses.

21 DR. ATRAKCHI: Very good. Thank you.  
22 Does the less than lifetime considerations which are



1 based on extrapolations of wrath data, take into  
2 account what Dr. Zeiger said, concerning the inducible  
3 enzymes? MGMT is known to be inducible in rats with  
4 increasing dose, whereas it is not in humans.

5 DR. KYRTOPOULOS: I have to come in  
6 here. May I? I am sorry. I do not want to  
7 monopolize.

8 DR. ATRAKCHI: No. Please, go ahead.

9 DR. KYRTOPOULOS: -- yes. Again, this  
10 is a question that drove me to look at the literature  
11 today. It is true that in the early days, there was a  
12 lot of work done to look for evidence of inducibility  
13 of MGMT in experimental animals. And this came  
14 because -- you know, the first methyltransferase that  
15 was discovered to -- which was repairing all this  
16 methylguanine was found in E. coli. It was called the  
17 ADA gene. And that was a highly inducible gene.

18 So, people started to look for  
19 equivalents of the ADA gene in animals. And there  
20 were papers where people administered  
21 diethylnitrosamine, for instance, to rats, and they  
22 did find an increase in liver MGMT. But do you know

1 the doses they used? One paper used five milligrams  
2 per kilo, and another 100 milligrams per kilo.

3 With dimethylnitrosamine, the one that  
4 I have found from the old papers, which have found  
5 some induction, the lowest concentration -- dose that  
6 had been used was one milligram per kilo of  
7 dimethylnitrosamine for four weeks.

8 When we did our study, where we exposed  
9 rats through the drinking water to doses of  
10 dimethylnitrosamine at the levels in the range which  
11 have been used by the -- in the Peto bioassay, we --  
12 excuse me -- and we had exposed for up to 180 days, we  
13 found a small increase in liver MGMT, between 15 and  
14 30 percent after 120 days of exposure to, at least,  
15 220 micrograms per day. For a human, that would  
16 correspond to 15 milligrams per day for a 70 kilo  
17 human.

18 So below those doses, we have found no  
19 evidence of a change in MGMT. So, I take these claims  
20 of inducibility of MGMT with a big pinch of salt.

21 DR. ATRAKCHI: Very well.

22 When exposure is considered, the low

1 dose range for nitrosamines? It is a big question.  
2 What is a low dose range for nitrosamines, I suppose  
3 to induce cancer?

4 DR. KYRTOPOULOS: Well, I would say --  
5 comparable to those likely to be experienced by  
6 humans? Having in mind that a lot of the experimental  
7 studies use higher doses, which may distort the  
8 picture. For me, that is the primary criteria. And  
9 coupled to that, I would say, following on from  
10 previous discussion, non-MGMT depleting.

11 DR. EISENBRAND: I agree totally with  
12 Dr. Kyrtopoulos, because we discussed this before, and  
13 it was always in relation to human exposure, more or  
14 less. That is low dose.

15 DR. ATRAKCHI: So, I mean, is there a  
16 number? What is a low dose?

17 DR. KYRTOPOULOS: Sure.

18 DR. ATRAKCHI: A range of low dose?

19 DR. KYRTOPOULOS: Yeah. If you -- if  
20 you look into, as we discussed yesterday -- when you  
21 look into human exposure, you end up with at max one  
22 microgram per person per day. That is a low exposure.

1 And that is what we discussed yesterday. And that was  
2 meant, actually. At this level, you will not find any  
3 induction, or any -- be it repair, or be it a  
4 metabolic enzyme. I do not think so.

5 DR. EISENBRAND: Yeah. I would even go  
6 a bit higher. I mean, even within the limits of the  
7 possible endogenous exposure that we, kind of,  
8 estimate with the tools that we have, which goes up  
9 to, maybe -- even a milligram total -- in total. That  
10 is a few micrograms per kilo, I guess -- tens of  
11 micrograms per kilo. If you compare this with the  
12 experimental studies which are being carried out, it  
13 is very low. Okay.

14 So, I would -- personally, I would call  
15 even those exposures low in a practical sense. But, I  
16 mean, this -- we should not attach to the use of the  
17 word, low, any significance in terms of risk  
18 associated with it. It is more low in terms of the  
19 mechanistic considerations that go -- that we go into,  
20 in order to assess the risk.

21 DR. EISENBRAND: I agree.

22 DR. ATRAKCHI: Is there any possibility

1 that activation occurs by enzymes, other than P450 and  
2 in organs other than the liver?

3 DR. KYRTOPOULOS: When we gave MDMA to  
4 Pettes monkeys, we saw large levels of methylation in  
5 the liver -- the stomach had even higher levels than  
6 the liver -- bladder, esophagus, pancreas, uterus, all  
7 had high levels of methylation -- and every other  
8 tissues we looked at measurable levels of methylation,  
9 in contrast to the rat, in which we see methylation  
10 primarily in the liver, and much less in the lung, the  
11 esophagus and the bladder. I leave -- blood is always  
12 methylated. But let's leave that out.

13 Now, why is it -- where is -- why is  
14 there this big difference? Is it that there are other  
15 enzymes in the tissues of the monkey? It is a  
16 possibility. My own working hypothesis is that,  
17 first -- liver, first pass clearance in the monkey may  
18 be a little bit less efficient than it is in the rat.  
19 So, a bit more dimethylnitrosamine escapes, and has  
20 the opportunity to reach post hepatic tissues.

21 When we gave dimethylnitrosamine  
22 together with -- sorry -- with ethanol, which is an

1 inhibitor of P450 2E1, which is the main enzyme which  
2 metabolism dimethylnitrosamine -- we found a small  
3 decrease in the methylation in the liver, but an  
4 enormous increase in post hepatic tissues. In the  
5 esophagus the methylation went up by 20 times.

6 Again, I do not know whether that means  
7 that metabolism in these post hepatic tissues is being  
8 carried out by other enzymes. I suppose the ethanol  
9 dose that we gave did not kill 2E1, it just suppressed  
10 it sufficiently to allow MDMA to through.

11 But, yeah. I do not know. I believe  
12 that in the rat esophagus, an enzyme which metabolizes  
13 dimethylnitrosamine have been discovered by Peter  
14 Swann some years ago. But -- I mean, there are other  
15 people much more expert on metabolism than myself,  
16 here. So, maybe they want to comment.

17 DR. HECHT: There is plenty of data  
18 from organ culture studies that extra hepatic tissues  
19 can metabolize nitrosamines.

20 DR. KYRTOPOULOS: But this is why a 2E1  
21 see -- or by a different mechanism?

22 DR. HECHT: I am not sure whether -- I

1 do not think in most cases we know what enzymes are  
2 involved. There are -- P450 is no doubt. But you  
3 know, there is plenty of data from organ culture  
4 studies with a variety of nitrosamines, that  
5 demonstrate ability to metabolically activate.

6 But for example, in the esophagus --  
7 the rat esophagus, which a common tissue affected by  
8 nitrosamines -- methylbenzyl nitrosamine is a good  
9 example. I mean, we know that the rat esophagus can  
10 metabolize methylbenzyl nitrosamine to get an O6  
11 methylguanine and other DNA adducts. But we do not  
12 really know the enzyme involved.

13 DR. KYRTOPOULOS: I think, Paul Kleihus  
14 [ph] has shown that it is mediated -- and he has also  
15 said that is made inside of P450, if I remember that  
16 correctly.

17 DR. HECHT: Probably a P450. Yeah. I  
18 do not think we know which one, though.

19 DR. ATRAKCHI: Are there certain  
20 genetic factors that are known to create higher levels  
21 of endogenous nitrosamines?

22 DR. KYRTOPOULOS: I do not think we

1 know anything about the factors which affect -- or  
2 almost anything. We know a little bit. But we really  
3 do not understand the determinates of endogenous  
4 nitrosation, whether they are environmental or  
5 genetic. At least, I do not know any such factors.

6 DR. ATRAKCHI: Yeah.

7 DR. HECHT: I think we know a little  
8 about diet, and --

9 DR. ATRAKCHI: Yes.

10 DR. HECHT: -- formation. I think  
11 there is a data on nitrosoproline inhibition by  
12 ascorbic acid, for example. I am pretty sure that  
13 data exists. In terms of the genetics, I do not think  
14 so.

15 DR. ATRAKCHI: Right. Would it be  
16 prudent to determine endogenous levels of nitrosamines  
17 in placebo groups in clinical trials for comparison  
18 with drug effect?

19 DR. KEIRE: So, yeah.

20 DR. ZEIGER: So -- quickly, I would  
21 just say, yes, because you are not measuring the drug  
22 affect against zero background. You are measuring



1 against the endogenous background.

2 DR. EISENBRAND: Yeah. I --

3 DR. KEIRE: And you should do --

4 DR. EISENBRAND: Sorry.

5 DR. KEIRE: Sorry. Yeah. You should  
6 do it -- you should do a crossover study, actually, on  
7 the same people, right? You know, so control as much  
8 as the biology as you can in the measurement.

9 DR. EISENBRAND: Yeah.

10 DR. KEIRE: Absolutely.

11 DR. EISENBRAND: That is a good idea,  
12 actually.

13 DR. KEIRE: Yeah.

14 DR. ATRAKCHI: Yeah. I think it is a  
15 must. The question is, probably that the number of  
16 molecules defines the of reactive diazonium or  
17 carbonium ions form. Does this -- doesn't this define  
18 the potency?

19 DR. HECHT: Yes. It should. And, I  
20 think, again, if you go back to the Peto study, you  
21 see -- a linear dose response, I think, down to very  
22 low doses, which is consistent with that.

1 DR. CRONIN: Yeah. I think this  
2 question may relate to -- there was some discussion at  
3 the end of yesterday's session, on whether we should  
4 be using weight -- or molar -- so nanograms, or  
5 micrograms, or molar values. So, yes. I would agree.  
6 It does. And it does bring into mind the use of the  
7 correct units for setting limits.

8 But regulatory units tend to be by  
9 weight, rather than by molar units. But for QSAR  
10 modeling, for instance, and for comparing between  
11 molecules, we would prefer to use molar units.

12 DR. KEIRE: Yeah. I mean, I guess, the  
13 comment I want to make is that, as a chemist, I am  
14 very comfortable with either of those, right? And  
15 molar units is just fine. But, I guess, in terms of  
16 public communication, people do not understand,  
17 sometimes -- you know, those terms. Or they do not  
18 think that way. And so -- but they do understand a  
19 weight. I do not even know if they even understand  
20 what a nanogram means, in terms of weight.

21 You know, but it is -- you know, in  
22 terms of communication, weight is easier to understand

1 by a bigger group of people.

2 DR. ATRAKCHI: TD50 and the CPDB does  
3 consider timetable data, whereas this is normally not  
4 done for the BMDL. How does this affect  
5 comparability?

6 DR. BUCHER: So, I looked at this  
7 question, and I -- it puzzles me a little bit, because  
8 I am not sure what timetable really referred to in  
9 either the enervation of the TD50 methodology, or in  
10 BMDL.

11 The Peto's group in developing the  
12 TD50s came up with a lot of corrections for comparing  
13 studies that had short period of dosing and various  
14 periods of observations. And maybe took into --  
15 difference in, whether tumors were considered  
16 incidental, and not necessarily fatal -- or considered  
17 fatal. Things that we have also used in NTP and  
18 earlier days.

19 I think, though, that most of the  
20 studies, now -- certainly, the one that we have done  
21 at NTP, have shifted over to doing -- calculating an  
22 individual survival based risk for each animal,

1 depending upon when it died in during the course of  
2 the study, whether it was during the study, or at the  
3 end of the study. And these risks that would then be  
4 taken into consideration in determining a survival  
5 adjusted incidence factor -- which is then the  
6 appropriate metric used in BMDLs.

7 I do not know that this is in any way  
8 shape or form possible to retrofit on the TD50  
9 calculations. But I have doubts -- serious doubts.  
10 But that is the only way I could understand that, that  
11 question might be interpreted.

12 DR. ATRAKCHI: The panel suggests that  
13 we should control nitrosamines in pharmaceuticals to  
14 zero exposure. However, proving zero is impossible  
15 given nitrosating agents -- nitrites are in water,  
16 excipients, so forth. Also, to show the absence of  
17 nitrosamines require an analytical limit. Shouldn't  
18 we be focused on the determining safe level of  
19 exposure, versus zero?

20 I think we have discussed this. But  
21 anyone would like to comment on this question?

22 DR. KEIRE: I guess I would say that

1 zero is preferred. When we cannot get that, we will  
2 take it below the acceptable intake.

3 DR. ATRAKCHI: Yes. I think that is  
4 the whole point -- is they should not be there. And I  
5 do not know if zero is a very absolute number. But --

6 DR. MCGOVERN: I guess, the main issue  
7 is -- it is difficult to prove zero.

8 DR. ATRAKCHI: Right.

9 DR. MCGOVERN: It is all based on your  
10 analytical --

11 DR. KEIRE: They are not --

12 DR. ATRAKCHI: It is all just the  
13 analytic method.

14 DR. KEIRE: They are not detectible by  
15 the appropriate analytical method.

16 DR. ATRAKCHI: Exactly. Right. Good.

17 The use of -- sorry -- if an API could  
18 potentially form a nitrosamine, wouldn't it be  
19 observed in toxicology studies, because endogenous  
20 formation is more probable than exogenous conditions?  
21 That is the question.

22 Any of the toxicologists or biologists

1 can answer this?

2 DR. EISENBRAND: I think that is -- if  
3 I may -- that is very difficult. We normally do the  
4 tox test in rats, or in animals, at least. Or -- and  
5 they are, of course, quite big differences between the  
6 rats and humans, in terms of nitrate, nitride, and  
7 nitrogen oxide metabolism, so to speak. So, rats, for  
8 instance, do not circulate in saliva nitrate as far as  
9 we know. And there are other differences.

10 So, I would not take this form an  
11 animal experiment as it guaranteed a nitrosation does  
12 not happen in humans. And that, of course, depends  
13 also from the nutritional status. You have a  
14 totally -- normally, a very different nutritional  
15 status between a rat experiment -- or rat populations  
16 and humans. Especially, with a -- of nitrate from  
17 vegetables. But.

18 DR. KEIRE: Yeah. So, I recall a  
19 comment that I heard that humans are a poor model for  
20 rat physiology. So -- you know, this is always going  
21 to be a gap that is present. You know, and the  
22 practical matter is sometimes you cannot test -- you

1 cannot do toxicology tests in humans. So --

2 DR. ATRAKCHI: The next question is the  
3 use or surrogate compounds has been discussed in  
4 relation to API related nitroso impurities, which  
5 could potentially form, in terms of setting limits and  
6 evaluating their carcinogenicity affect. When it  
7 comes to determination and control of such API related  
8 nitroso impurities, is the use of surrogate compound  
9 in method development, validation, and quantification,  
10 recommended? If yes, what aspects would you recommend  
11 that should be taken into account regarding this  
12 election of the appropriate surrogate, in terms of  
13 uncertainty factors, or setting method parameters, and  
14 etcetera?

15 I guess, this is specifically in  
16 relation to an API related nitroso. What surrogates,  
17 I guess, would be appropriate in setting the limits.

18 DR. CRONIN: I am not sure -- quite  
19 sure who -- or the surrogate means a read-across  
20 analog, which takes us back to the discussions we had  
21 earlier. In which case, it is one way we can  
22 demonstrate formalities of mechanism action and

1 structural similarity. Or whether there is some  
2 thoughts of the surrogate may mean it has the same  
3 drug action -- similar API. In which case, is a very  
4 different scenario.

5 That is how I start to think about  
6 answering this question.

7 DR. ATRAKCHI: Thank you. I think the  
8 next one -- I will read it. This is -- it is a follow  
9 up from yesterday's discussion about whether  
10 acceptable intakes for more complex higher molecular  
11 weight in nitrosamines should be addressed differently  
12 than low molecular weight nitrosamines, such as MDMA  
13 and MDEA. Specifically, in the case where a novel  
14 higher molecular weight nitrosamine is encountered in  
15 a drug product for which the carcinogenic potency is  
16 unknown, should the default AI -- 18 nanogram per day  
17 for EMA, or 26.5 nanogram per day from FDA -- be  
18 applied on a molar basis, rather than a mass  
19 basis -- parenthesis, 259 picomoles equals to 26.5  
20 nanogram of NDEA -- to account for active site of NMO  
21 group, rather than the molecule's mass? AI based  
22 nitrosamines can have two to five times molecular



1 weight than the simple nitrosamines.

2 DR. HECTH: Sure. On a molar basis.  
3 It makes sense. It is the nitroso group, and the  
4 carbons that are alpha to it, that are critical in  
5 determining whether there is going to be activity or  
6 not. And the rest of the molecule, will -- sure, will  
7 play a role in the activity. But I think, at a first  
8 approximation, you would want to go on the molar  
9 basis, not just by molecular weight.

10 DR. ATRAKCHI: Any other thoughts?  
11 Thank you, Dr. Hecht.

12 DR. CRONIN: Yeah. I -- again, we are  
13 back to considering the whole question of the limits,  
14 and the unit in the limit. And really, to answer this  
15 question, you would have to say, is the -- my  
16 understanding of the question -- I apologize if I am  
17 misinterpreting -- is the limit, in itself,  
18 protective, and is that the most conservative limit we  
19 want, regardless of whether it is calculated in  
20 nanograms or molar value.

21 So, that is how I would think about it,  
22 just in terms of being precautionary.

1 DR. ATRAKCHI: Right. The next  
2 question is, it appears from the discussion that  
3 read-across, QSAR, and Ames data will not be  
4 sufficient to classify novel nitrosamines as low or no  
5 carcinogenic potential. What studies would the  
6 panelists recommend to definitely classify a novel  
7 nitrosamine as low or no carcinogenic potential?

8 DR. CRONIN: Again, I hope I was not  
9 that pessimistic about how we can use QSAR and  
10 read-across. I think there are possibilities for  
11 classifying a compound using good read-across,  
12 supported by good QSAR modeling, which could be  
13 modeling of the metabolic step, for instance, and Ames  
14 test data.

15 I think the caution I had was that we  
16 required more evidence -- more certainty to be able to  
17 classify something as no or low toxicity, regardless  
18 of any point. So, I think there are possibilities to  
19 do it. I think we can be guided by the structural  
20 activity, here, as well as other information.  
21 Otherwise, you will be in the situation where  
22 everything you want to classify as no, or low toxicity

1 will have to be tested. I think we can move away from  
2 that paradigm.

3 DR. BUCHER: So, Dr. Cronin also  
4 mentioned the fact that problem formulation is very  
5 important in that kind of situation. And I would  
6 agree that -- you know, you have to, sort of, play out  
7 the whole possibilities associated with a potential  
8 contaminant that you are -- that is not recognized yet  
9 as to whether it is a carcinogen or not. Look at the  
10 potential concentrations of the material, and then,  
11 make some expert judgments based on -- you know, what  
12 is known about the chemistry of the material.

13 But I -- you know, as an organization  
14 that does two year bioassays, faced with the potential  
15 problems of many, many nitrosamines coming down the  
16 pipe, it is just not an attractive solution.

17 DR. ATRAKCHI: Any other questions that  
18 I may have missed, or any that came from the  
19 attendees -- my colleagues who are following on those?  
20 Or any other questions from the FDA to the panelists?

21 I think, if none, it is a -- we are a  
22 little bit early -- earlier than with the time allowed

1 for this workshop. But I think to make things --  
2 there is one question.

3 If a novel nitrosamine tested negative  
4 in the Ames test, what modification to standard  
5 protocols would you recommend to make sure it is an  
6 Ames negative?

7 We have discussed changing the S9 from  
8 the rat to mouse or hamster. Any other  
9 recommendations?

10 DR. ZEIGER: So -- yeah. This question  
11 has come up before. Right. And if I saw a  
12 nitrosamine function on the chemical, I would do a  
13 quick test using just TA1535, TA100, and rat liver S9.  
14 That seems to be the most useful combination for  
15 detecting nitrosamines.

16 The rat is less sensitive -- rat S9 is  
17 less sensitive than mouse S9. And I think, also a bit  
18 less sensitive than hamster S9. And all the  
19 nitrosamines that I am familiar with are positive in  
20 the TA1535, TA100 series of strains.

21 So, that would be a quick and easy  
22 test. You know, S9, two strains. If it is negative,

1     there, I would go to the wider test battery. But if  
2     it is negative there, I would not expect it to be  
3     positive in the wide test battery, unless there was  
4     some other functional unit on the -- some other  
5     mutagenic unit further down the molecule that is not  
6     associated with the nitrosamine function.

7                     DR. ATRAKCHI: Thank you, Dr. Zeiger.

8                     DR. GUTTENPLAN: I have a comment.

9                     DR. ATRAKCHI: Yes, please.

10                    DR. GUTTENPLAN: So, probably 30 years  
11     ago we reported that the potency of nitrosamines in  
12     the Ames test can be greatly increased by dropping the  
13     PH. It turns out that the intermediate -- the  
14     hydroxy -- alpha hydroxy nitrosamine is much more  
15     stable at acidic pHs, and therefore, you get much more  
16     permeating into the bacteria.

17                    So, if you want to start playing with  
18     conditions of the assay, dropping the pH to six, or  
19     six point five, for a nitrosamine, should greatly  
20     increase the sensitivity. And --

21                    DR. ZEIGER: Dropping the PH to six  
22     would kill a lot of the salmonella on the plate.

1 DR. GUTTENPLAN: It works. We did it.

2 DR. ZEIGER: Okay. Because --

3 DR. GUTTENPLAN: It is published.

4 DR. ZEIGER: Okay.

5 DR. GUTTENPLAN: They were only exposed  
6 during the pre-incubation. And then, of course, they  
7 get -- it gets diluted into the top auger.

8 DR. ZEIGER: Okay. We have experiences  
9 where once you go down to six or below, you are  
10 getting toxicity from the pH affect, whether it be a  
11 pre-incubation, or a plate test.

12 DR. GUTTENPLAN: Yeah. I have to go  
13 back and look at the publication. Maybe, we went to  
14 six point five, rather than six.

15 But anyhow, it is out there. And it  
16 was confirmed by a group in Japan. And -- so it is  
17 just if you want to play with conditions, you can  
18 probably make the Ames test more sensitive. And as  
19 Dr. Zeiger mentioned, hamster S9, is certainly better  
20 than rat S9, and probably better than mouse S9.

21 DR. ZEIGER: Well, in my experience,  
22 the mouse was better -- equivalent or better than

1 hamster. It is -- but this is primarily with a series  
2 of cyclic nitrosamines. I have not compared them to  
3 any extent with the aliphatic.

4 DR. GUTTENPLAN: Yeah. I think there  
5 is literature out there on that.

6 DR. ZEIGER: There probably is. Yeah.

7 DR. ATRAKCHI: Very good. Thank you,  
8 very much for a very comprehensive and valuable  
9 information that you all have provided us to consider,  
10 and to think about.

11 I think, to summarize, mainly, is that  
12 in terms of nitrosamine classification, the parameters  
13 we suggested -- or proposed -- or put on the table,  
14 they all are important, whether it is the potency --  
15 we should take that into consideration -- the chemical  
16 structure, as well as reactivity. These are all  
17 parameters that are important for us in order to make  
18 a classification of nitrosamines.

19 But, also, what is considered --  
20 whether a classes specific limit -- whether it is the  
21 18 nanogram per day, suggested by EMA, or any other  
22 number -- that could be used, as well. But it needs

1 to have some basis why if one number fits all.

2 We also discussed the issues of risk  
3 assessment of multiple nitrosamines in one that will  
4 be present -- or found in the drug substance or drug  
5 product, and we understood that the -- they need to be  
6 treated, basically, whether it is one, or 10, or five.  
7 They need to follow whatever the conservative approach  
8 as one potent nitrosamine -- whether it is the NDMA or  
9 the NDEA, because the affect is additive.

10 We also discussed the less than  
11 lifetime approach, and there is a great deal of  
12 information there to consider for the less than  
13 lifetime consideration with nitrosamines.

14 And the QSAR -- the QSAR is really  
15 the -- probably the future. But there are many gaps  
16 that needs to be addressed for the QSAR of  
17 nitrosamines, in particular. Things to consider is  
18 reactivity -- is the behavior of the diverse nature of  
19 the chemistries of nitrosamines in vitro and in vivo,  
20 and the slight modification in structure that could  
21 lead to significant different in biology of that  
22 particular nitrosamines.



1 But it is a tool that needs to take a  
2 lot of things into consideration, and a lot of the  
3 data that is available, out there. But I believe  
4 there is more to do with the QSAR and the read-across.

5 The topic of endogenous, whether it  
6 should be considered -- the exogenous as well as --  
7 and/or endogenous levels of nitrosamines when we  
8 assess the risk assessment for the nitrosamines as  
9 impurities in drugs. The endogenous formation  
10 is -- seems to be, based on the discussions of the  
11 last two days -- is very important parameter that  
12 needs to be addressed, and it is lacking in good and  
13 accurate information.

14 But that is something for the future,  
15 that should be -- that studies should be designed and  
16 should be considered and should be conducted. It is  
17 not something we can do immediately and use the  
18 information from that.

19 In terms of the other exogenous -- the  
20 dietary -- that is another one that depending on the  
21 diets, different parts of the world, different parts  
22 of the same country -- it is also a difficult -- but

1 it more manageable than, perhaps, data from the past,  
2 as well as data that can be collected and some -- a  
3 lot of publications do exist -- could be considered.

4 But ultimately, the way that I think  
5 it ended -- the discussion on this -- is that we do  
6 need to pay attention. If we ignore both of those big  
7 contributors to the nitrosamines, then it is the  
8 quality of the drug -- of the medicines that are taken  
9 by patients that needs to be considered, in terms of  
10 limiting the amounts of nitrosamines in the  
11 pharmaceuticals -- in the medicine.

12 And again, the last two questions were  
13 on chemistries and manufacturing. And it became  
14 evident that nitrosamines -- it is all about  
15 chemistry. It is all about -- from the beginning, the  
16 awareness and the wholistic approach to understanding  
17 what is the synthetic pathway -- what is the  
18 particular molecular that one want to synthesize and  
19 manufacture. There is a lot of -- it is not only it.  
20 But it is everything around it -- all the excipients,  
21 all the temperatures, all the pH, and whatever the  
22 intermediates -- everything needs to be considered

1 along the path of formation of that API, and  
2 ultimately, the drug product, as well as beyond that.  
3 It is the post marketing, the packaging -- how is  
4 it -- where is it going -- in what conditions it is  
5 going.

6 So, I think, in my mind, there is a  
7 great deal that can be done and controlled right from  
8 the beginning on the chemistry and in manufacturing,  
9 before we get to the problems of -- we found  
10 nitrosamines in drugs and how do we do risk  
11 assessment. It need -- all of this needs to be  
12 addressed before we try to mitigate and see, well,  
13 what can we do, can we go to one in hundred thousand,  
14 can we go less than that, because this drug is  
15 essential, it needs to be on the market, and needs --  
16 we cannot take it off.

17 In my mind, there are a lot of tools.  
18 There is a lot of things that can be done to prevent  
19 and minimize the formation of nitrosamines in drugs  
20 before we get to all the way and trying to see -- and  
21 try to really grapple on the issues of what can we do,  
22 it has to be there, it is going to be there, what can

1 we do, and what is the risk for the patients.

2 With that, I think, we really  
3 appreciate your contribution and your participation in  
4 this workshop. It has been valuable for the agency,  
5 and for the attendees to listed to your expert  
6 scientific opinions on the topic.

7 Thank you, very much. And this  
8 workshop, as we indicated in the beginning, it is  
9 recorded, and it will be available by the end of this  
10 week, as well as the two presentations, and  
11 Doctor -- both, Dr. King, as well as Dr. Eisenbrand,  
12 and Kyrtopoulos slides will be available at the end of  
13 the day today.

14 Thank you, so much, for participating.

15 DR. KEIRE: Thank you, Dr. Atrakchi,  
16 for your -- great moderation.

17 DR. ATRAKCHI: Thank you.

18 DR. KEIRE: Yeah. And the panelists,  
19 you guys are all great. I appreciate you brining all  
20 this knowledge together. It is very helpful.  
21 Appreciate it.

22 DR. ATRAKCHI: Thank you.

1 DR. KYRTOPOULOS: thank you.

2 DR. ATRAKCHI: Thank you, all. Bye-  
3 bye. Thank you.

4 (Whereupon, the meeting concluded at  
5 2:12 p.m.)

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2 I, IRENE GRAY, the officer before whom the  
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