

1       The Nitrosamines as Impurities in Drugs; Health Risk  
2                   Assessment and Mitigation Workshop

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6                   Moderated by Dr. Aisar Atrakchi  
7                   Monday, March 29, 2021  
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11                   Food and Drug Administration (FDA)  
12                   Office of New Drugs  
13                   White Oak Campus  
14                   10903 New Hampshire Avenue  
15                   Silver Spring, MD 20903

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21   Reported by:    Irene Gray  
22   JOB No.:        4377489

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

2 List of Attendees:

3 Dr. Gerhard Eisenbrand

4 Dr. Soterios Kyrtopoulos

5 Dr. Joseph Guttenplan

6 Dr. Errol Zeiger

7 Dr. John R. Bucher

8 Dr. Jerry M. Rice

9 Dr. Stephen S. Hecht

10 Dr. Richard H. Adamson

11 Dr. Michael DiNovi

12 Dr. Aisar Atrakchi

13 Dr. Sruthi King

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

2 MS. PAINTER: Hello, everybody, and  
3 thank you so much for joining this two-day workshop on  
4 Nitrosamines as Impurities in Drugs. Before we get  
5 started with Day 1, we did want to just go over some  
6 house rules, just things to keep in mind as we go  
7 through this workshop.

8 For those who are not speaking, please  
9 be sure to keep your phone or computer audio on mute.  
10 All attendees will be muted, and only the panelists  
11 who will be speaking in today's discussion will have  
12 the ability to unmute.

13 As far as using the video feature, only  
14 the panelists that will be engaging in today's  
15 discussions will have their video features turned on.  
16 So, if you are not speaking, please be sure to have  
17 your video feature turned off. And regarding  
18 questions and discussions during today's workshop,  
19 please utilize the QA to submit any questions that  
20 you'd like to have answered during today's workshop  
21 using the QA feature. You may not automatically  
22 receive a response from us, but we do have a team of



1 moderators reviewing the questions, and then they will  
2 be submitted and addressed as time allows during this  
3 workshop.

4 If you are a panelist who will be  
5 speaking, please check your chat feature as the host  
6 will be prompting you when it is time for you to  
7 present.

8 And last, I just wanted to let  
9 everybody know that this workshop today and tomorrow  
10 will be recorded, and the slides will be made  
11 available on the FDA webpage after this workshop.

12 Thank you.

13 DR. ATRAKCHI: Can everybody hear me?

14 MS. PAINTER: Yes, we can.

15 DR. ATRAKCHI: Thank you. Good  
16 morning, good afternoon, and good evening. My name is  
17 Aisar Atrakchi. I am a pharmacology/toxicology  
18 supervisor in the Division of Psychiatry, Office of  
19 Neuroscience in the Center for Drug Evaluation and  
20 Research, CDER. I am a member of the CDER Nitrosamine  
21 Task Force and one of the organizers of this workshop,  
22 as well as the Moderator.

1 I would like to welcome all of you to  
2 this workshop on Nitrosamine as Impurities in Drugs.  
3 There are over 3,500 registrants for this workshop.

4 Over the past 2-1/2 years since the  
5 detection of nitrosamines in medicines, both the  
6 regulators and the pharmaceutical industry have been  
7 challenged with the many aspects of this public safety  
8 incident. There is a discontinuity in our knowledge  
9 of nitrosamines since most of the research and science  
10 was conducted 50 years ago. In order to make the best  
11 scientifically-based decisions on the safety and risk  
12 assessment and mitigation, we have gathered the most  
13 qualified nationally and internationally recognized  
14 scientists and researchers in this field to inform us  
15 of previous foundational knowledge and the current  
16 state of the art practices.

17 We have prepared a number of critical  
18 questions for the panelists to discuss and answer over  
19 the next two days. Before we begin the presentations,  
20 I would like to remind everyone this is a scientific  
21 workshop. No policy or regulatory comments will be  
22 discussed. So, please limit your questions to the

1 science and to the discussions. You may send a  
2 clarifying question as just mentioned to you or  
3 comment to the chat box or the Q&A box, and we will  
4 attempt to answer as many as possible during the  
5 discussion of the particular question or at the end of  
6 the day. However, please note that the objectives of  
7 this workshop are for the experts to discuss and  
8 deliberate on the questions the Agency has provided to  
9 them.

10 Without further delay, we begin with  
11 the first presentation by Professor Gerhard Eisenbrand  
12 to give us an overview on the Chemistry and the  
13 Toxicity of Nitrosamines to set the stage.

14 This will be followed by a presentation  
15 by my colleague Dr. Sruthi King, who will provide the  
16 background on the Nitrosamine Contamination Incident  
17 in Drugs that was identified in June of 2018.

18 Biographies of all of the panelists  
19 have been posted on the FDA website for your  
20 information, and as also mentioned earlier, this  
21 workshop will be recorded and will be available soon  
22 after the workshop.

1                   And with that, please, we will begin  
2 with Dr. Eisenbrand. Thank you.

3                   DR. EISENBRAND: Thank you very much,  
4 Dr. Atrakchi. And I may start with stating that my  
5 presentation reflects my personal views as a retired  
6 professor of fruit chemistry and toxicology, and I may  
7 admit it may be perhaps be biased a bit by my  
8 scientific experience in the history of field of  
9 N-Nitroso chemistry and biology for the last 50 years  
10 or so. So, for some time the subject has been thought  
11 to be adequately explored or for some people, even  
12 over-explored, but I myself never shared this opinion,  
13 mainly because there are definitely knowledge gaps,  
14 especially with respect to the problem of in-vivo  
15 N-nitrosation.

16                   Now it has resurfaced as a consequence  
17 of discovering seemingly unexpected drug contamination  
18 originating from changes in a production process  
19 introduced without awareness of the risk to generate  
20 nitrosamine contamination. This exemplifies the need  
21 of adequate safety checks of processes based on  
22 scientific knowhow. Now, after realizing that this

1 appears to be quite a general problem, we are faced  
2 with increasing complexity with respect to the  
3 potential causes. There is another point. And as I  
4 will outline, the second field of complexity is  
5 connected to the fact that human physiology provides  
6 ample potential for endogenous formation of nitroso  
7 compounds. And this needs to be evaluated as well  
8 when assessing respective health risks occasionally  
9 associated with APIs carrying the risk to become  
10 nitrosated.

11 Now, could I get the next slide please?  
12 This slide just shows the discovery, history, and  
13 earlier research. There have been acute intoxication  
14 reports, several. The first one was by Freund who  
15 described clinical manifestations and studies of acute  
16 human intoxication resulting in parenchymatous  
17 hepatitis, and this was later on almost -- or even  
18 much later then it was again taken up. And toxic  
19 properties of dimethylnitrosamine were described  
20 because dimethylnitrosamine had been proposed at that  
21 time as an industrial solvent. So, it turned out for  
22 those two, Dr. Barnes and Magee that the intoxication

1 symptoms, rescinded to some extent intoxication with  
2 pyrrolizidine alkaloids from which it was known  
3 already that these were hepatocarcinogens. So, it was  
4 very logical to see whether nitrosodimethylamine might  
5 also be a hepatic carcinogen or a carcinogen all  
6 together, and this was more or less against the  
7 current views at that time because this was a very  
8 well water-soluble and very low molecular weight  
9 compound contrary to all the other known carcinogens  
10 like polycyclic aromatic hydrocarbons and so on.

11 But to cut a long story very short,  
12 this indeed has been shown to be the case, and this  
13 later was repeated by a German group, and these  
14 authors also tested the next analog, that was  
15 dimethylnitrosamine, showed that it even was more  
16 carcinogenic. And then within a relatively short  
17 time, the group of Peter Magee showed that  
18 dimethylnitrosamine was a methylating agent,  
19 methylating DNA very effectively.

20 Next please. So, again cutting a long  
21 story short, there was then a tremendous amount of  
22 research, biological and chemical. And I just

1 mentioned two publications that reflect the results of  
2 all this research. One is what was long called in  
3 German The Nitrosamine Bible that was this publication  
4 here as structure activity related and dose response  
5 related, very extensive investigation of 65 N-nitroso  
6 compounds published in 1967. And then another time  
7 John showed the megamouse rodent studies that have  
8 been evaluated very formally by the group of Peto and  
9 his coworkers with a very detailed dose response,  
10 details especially for dimethyl- and  
11 diethylnitrosamine.

12           Next, please. So, to get a summary of  
13 the biological activities of NOC shows NOC means  
14 N-nitroso compounds. It shows that over 90 percent,  
15 more than 300 nitroso compounds are known to be  
16 carcinogenic and in animal experiments, so if you find  
17 a new compound or a new structure, the probability is  
18 relatively high that this may be a carcinogen, but  
19 there are some structural activity showing that one  
20 can get a little bit more power into the predictions  
21 of carcinogenic potency. The most investigated  
22 compounds, dimethyl- and diethylnitrosamine and also

1 the tobacco-specific compounds use tumors in a very  
2 wide spectrum of animal species up to subhuman  
3 primates, and there is no species that is found to be  
4 resistant. Structured community studies have helped  
5 to conclude on structural elements that are  
6 responsible for carcinogenicity, and those vice versa  
7 that may abrogate carcinogenicity. And there is a  
8 characteristic feature of many of these nitroso  
9 compounds that they may induce at the right dosage  
10 quite specific organotrophic activities. Almost all  
11 organs of experimental animals that have been used are  
12 listed here.

13           The last one is that the bioactivation  
14 of nitroso compounds that the interaction is crucial  
15 induced in targets proceeds basically similar in  
16 animals and in human tissues.

17           Next please. So, the metabolism is  
18 very well investigated, and it shows that the most  
19 critical event is the alpha-C hydroxylation of nitroso  
20 compounds. Nitrosamines in this case where you see  
21 that after the alpha-hydroxy group has been introduced  
22 by cytochrome p450, then the enzymes, and aldehyde is



1 split off, and you get an alkylating intermediate,  
2 either diazonium ion or a -- cation, which then is  
3 able to alkylate nucleophilic sites in the DNA at  
4 different DNA bases, including also phosphates by the  
5 way. Metabolism is not necessary for the direct-  
6 acting nitroso compounds like here shown, the alkyl  
7 nitrosoureas that just alkylate by direct  
8 decompensation, often catalyzed by basic media.

9           Next please. So, there is a group of  
10 rules concerning prediction of carcinogenic activity  
11 from structures. Since the alpha-C hydroxylation, the  
12 metabolic one matters so much that it is easy to  
13 conceive that if you put in branching in the other  
14 position, you will inhibit or at least decelerate the  
15 metabolic activation. That is definitely the case of  
16 branch compounds, and the alpha position branch  
17 compounds are less carcinogen than the stretching  
18 ones. And this goes up to the point that you have  
19 tertiary butyl branch. They are noncarcinogenic.

20           The second point of consideration also  
21 is that if you have a tertiary butyl substituent in  
22 this position, then you very often have also a slowing

1 down of nitrosation because it leads to some extent  
2 the nitrosation.

3                   Next slide. So, compounds that are  
4 known to be relevant for human exposure versus nitroso  
5 compounds are shown here in this selection. There are  
6 volatile compounds. This has this reflection in the  
7 analytical determination of these compounds that are  
8 basically determined by a purification at the  
9 destinate step. Dimethylnitrosamine up to  
10 nitrosomorpholine. These are the carcinogenic or even  
11 highly carcinogenic ones. Nitrosopyrrolidine is  
12 somewhat less active than the short chain ones,  
13 nitrosomorpholine, and then there are non-volatilized  
14 nitrosodiethylamine known to be a contaminate of  
15 cosmetics, or they have been a contaminant of  
16 cosmetics. And then the nitrosoamino acids, most of  
17 them are noncarcinogenic with the exception of  
18 nitrososarcosine that is a weak carcinogen. The  
19 reason for this non-carcinogenicity is believed to be  
20 the very good water solubility and the ionization  
21 under physiological pH, and this is also true for  
22 compounds that may contain amino groups, ionizable, or

1 protonable amino groups that may then if the compound  
2 is protonized also inhibit or at least make this  
3 option quite slow.

4 Next slide. So some words to the  
5 basics of formation of N-nitroso compounds.

6 Next please. So, this depicts -- it is  
7 a busy slide, but it depicts more or less what has  
8 been published already in 1975 by Sid Mirvish and  
9 depicts rates and the factors that are important for  
10 the rates. First of all, it is important to realize  
11 that the nitrosating agent itself is  $\text{N}_2\text{O}_3$  in aqueous  
12 acidic solution, and the formation of this  $\text{N}_2\text{O}_3$  is  
13 going through the interaction of two molecules of  
14 undissociated nitrous acid. So, the formation of  
15 nitrous acid is favored by proton concentration. The  
16 more acidic the milieu is, the more nitrosating agent  
17 is available. On the other side, it is only the  
18 unprotonated amino nitrogen that can be nitrosated, so  
19 in other words, the results is then this bell-shaped  
20 curve you see on the righthand side of the panel that  
21 shows the pH dependency of the nitrosation rates in  
22 short.

1                   The second point also to take into  
2 consideration is that the pK(a) value of the amines  
3 very strongly determines the nitrosation rates, saying  
4 that high pK values, strongly basic amines are  
5 relatively much less easily nitrosated than weakly  
6 basic amines. The examples shown here are  
7 dimethylamine for a strongly basic one and for  
8 instance morpholine or piperazine for a weakly basic  
9 amine.

10                   Next please. This is also shown again  
11 here. On the left-hand side, you will see what you  
12 have seen directly before, but on the right-hand side,  
13 there is a collection of data showing that this  
14 in vivo nitrosation can be shown interactions by  
15 giving appropriate dosages of amines, not nitrosamines  
16 but amines, and of nitride. And in that case, the  
17 green field here, the green area, shows the high pK(a)  
18 amines that are not producing enough nitrosamine in  
19 the acidic medium of the gastric milieu of the  
20 stomach, whereas the ones that are within this red  
21 field here, the low pK(a) amines, the weakly basic  
22 amines, they have been shown like nitroso

1 methylbenzylamine or nitroso piperazine, they have  
2 been shown to yield enough nitroso compound in vivo,  
3 in the stomach to induce the same tumors as what would  
4 be seen when getting the nitroso compound itself. So,  
5 that's the first information about this in vivo  
6 situation that has been tested many years ago.

7           Next please. So, as another point of  
8 importance, and that is if you remove the possibility  
9 of the amine to get protonated, for instance by  
10 interaction with formaldehyde, then the nitrosation is  
11 no longer dependent on the acid medium, but it can  
12 also directly go on in neutral or either basic milieu,  
13 and that is a problem that has been faced mainly in  
14 occupational exposure situations. For instance, with  
15 the metal industry, the cutting fluids that are  
16 normally weakly basic. Where nitrogen oxides in the  
17 industrial environment directly interact with amines  
18 and form nitroso compounds, and this may also happen  
19 with nitride.

20           Next please. So, to get this together,  
21 I have not mentioned yet the primary amines that also  
22 to some extent might directly react in an acidic

1 medium for instance to form diazonium ions, so in  
2 other words, they may also form electrophiles that  
3 could be available for interacting with DNA for  
4 instance or biological material. However, the rates  
5 are much slower than those for secondary amines, which  
6 normally nitrosate quite rapidly under the conditions  
7 I have just outlined before. And of course, as  
8 mentioned in basic or nonaqueous media, there is also  
9 a rapid possibility of rapid interaction with  
10 nitrosating agents, since the protonation is not  
11 completed. Most tertiary amines form also nitroso  
12 compounds by a process called dealkylating  
13 nitrosation. Normally, a few significant exceptions  
14 at much smaller rates, and then they have the  
15 catalysts, formaldehyde, and other carbonyl compounds  
16 that may interact also. Halogenides and thiocyanate  
17 for instance are acting as catalysts, whereas  
18 compounds that are scavenging nitrosating agents, like  
19 ascorbates, tocopherols, and phenolics, for instance  
20 flavonoids, they are normally considered as inhibitors  
21 of the nitrosating reaction.

22 Next please. Again, quite a busy

1 slide, but it's important. This is a relevant  
2 tertiary amine. It is nicotine. Nicotine undergoes  
3 quite easily nitrosation, dealkylating nitrosation,  
4 and in response to the ring opening reaction or  
5 demethylating reaction that is going on, we get three  
6 different compounds that are shown here, NNN, NNA, and  
7 NNK, which is very involved in tobacco-specific  
8 nitroso compound.

9           And the lower part of that slide shows  
10 the metabolic activation, which is well known and very  
11 well investigated, methylating or into a  
12 ketobutyrate agent that interacts with the DNA.  
13 Finally, and on the utmost right-hand side, you will  
14 also see a reaction that might be called a  
15 detoxification reaction because the keto group  
16 undergoes to some extent partial reduction to the  
17 alkyl ion, and the alkyl is then excreted in the urine  
18 as the corresponding glucuronide. Now, NNK and NNA  
19 have been rated to Group 1 carcinogens by IARC. So,  
20 they are carcinogenic to humans because there is  
21 sufficient evidence for carcinogenicity in animals,  
22 and there's strong mechanistic evidence also in

1 exposed humans. And there is another aspect that also  
2 is quite important for human exposure, and that is --

3           Next slide, please. That we also have  
4 passive exposure to tobacco smoke, very well  
5 investigated by my dear colleague, Stephen Hecht, who  
6 has been working very intensely on these subjects.  
7 And the base of the biomarkers excreted in the urine  
8 of nonsmoking, exposed people, starting with  
9 transplacental exposure already and measured for  
10 instance in urine of newborns and other exposed  
11 population that may be passively exposed to so-called  
12 secondhand smoke. You see that it is about 1 to 5  
13 percent of those in smokers as being rated there. So,  
14 it is quite significant.

15           Next slide please. So, let us just  
16 have a short walk-through nonfood products, cosmetics  
17 as the first example, and personal care products have  
18 been found many years ago already that these are  
19 providing exposure maybe by nitroso-methylalkylamines  
20 and some others that are listed here up to  
21 nitrosomorpholine and long chain components. The main  
22 problem there was insufficient purity of basic



1 materials. In other words, it has been so rapidly  
2 thereafter when people became aware of this problem,  
3 and also there have been some nitrosating  
4 preservatives like bronopol or bronidox that are  
5 transnitrosating or nitrosating agents.

6           Next slide, please. So, it's clear  
7 that mitigation based on the knowledge was quite  
8 effective. Purity was determined by purity  
9 specifications, maximum content of nitrosamines. And  
10 these all ended finally up an estimate of well-known  
11 exposure, systemic exposure by dermal application of  
12 cosmetics lower than 0.05 micrograms per person per  
13 day.

14           Next, please. One short word to the  
15 occupational exposure also known since many years.  
16 One of the courses I have already alluded to is the  
17 use of nitride as a corrosion inhibitor or the  
18 interaction of nitrogen oxides in an industrial  
19 situation with the amines that are present in cutting  
20 -- for instance in metal cutting fluids. And this  
21 contamination went up to PPN, even high PPN values.

22           Next slide, please. Again, the

1 logistics of mitigation are just written here. They  
2 are spelled out in the Technical Rules for Hazardous  
3 Substances. The last edition I think is 2018 in  
4 Germany or whatever it is called, TRGS 522. So, these  
5 are the mitigation measures recommended. No use of  
6 nitrite as a corrosion inhibitor, using nitrosation  
7 inhibitors, and replace chemicals giving rise to  
8 carcinogenic nitroso compounds by those that do not  
9 give rise to carcinogenic compounds. And that  
10 principal or that strategy has been called the  
11 strategy between "safe amines."

12           The next slide shows -- I think an  
13 example for that you see on the left-hand side  
14 compounds that are used, for instance, in rubber  
15 industry for vulcanization of rubber. These are  
16 thiuram disulfides, and they under good protection  
17 conditions, they would then generate  
18 dimethylnitrosamine or nitrosomorpholine at the lower  
19 example case. And on the right-hand side, you'll see  
20 what we can do for prevention or mitigation. These  
21 compounds can also equally be used or almost equally  
22 be used for technical purposes, and that falls along

1 carcinogenic nitrosamine within that green circle, and  
2 the same is true for the lower line examples shown  
3 here. Alpha branch nitrosopiperidine or N-  
4 methyl-nitrosopiperazine, which is not known to be  
5 carcinogenic contrary to dinitrosopiperazine, which is  
6 quite a strong carcinogen. Okay. So, that is the  
7 example of safe amines.

8           The next, please. We go now to the  
9 technical rules a little bit more in detail because I  
10 want to show you regulations as written in the TRGS  
11 552. There is a tolerance and acceptance  
12 concentration. For instance, in the air, that is  
13 being inhaled at working places. At the moment it is  
14 0.75 micrograms per cubic meter is the tolerance and  
15 one-tenth of it or 0.075 micrograms per cubic meter is  
16 the acceptance concentration also, not only for the  
17 individual nitroso components but also for the sum of  
18 it if there are several components in the air found.

19           Next please. Now the last word on the  
20 exogenous is exposure to food. They have the  
21 nutrition exposure. Interesting to see, but the very  
22 first incidence reported in the literature was in an

1 animal meal based on fishmeal that had been treated  
2 with nitrite. In that case, hepatotoxic factor, which  
3 at that time was not known, has been identified and  
4 later more or less identified because it was a very  
5 high contamination that it was dimethylnitrosamine,  
6 and truly enough the animals got liver toxicity. So,  
7 this, of course, triggered almost an avalanche of  
8 research into foods because of course animal-based  
9 foods are very often cured or smoked or at least  
10 should be an expected formation of nitroso compounds,  
11 and this research was long hampered by the relatively  
12 insufficient analytical methods. Finally, developed  
13 the thermal energy analyzer (TEA) and later on of  
14 course, and that is the present state of the art, is  
15 the coupling of chromatographic separation methods  
16 with multiple mass spectrometry for identification.

17 Next please. So, the processing  
18 methods -- because nitroso compounds in foods are  
19 process-related contaminants, which are potentially  
20 responsible are curing with nitrate or nitrite. So,  
21 reduction of these could help. Then, the addition of  
22 literature, then for smoked food, lowering of the NOx

1 content in the smoke with which foods are treated.  
2 Drying or kilning of malt by direct firing techniques  
3 has been found to be shown to nitrosamine formation.  
4 And in rare cases also packaging by migrational  
5 nitroso compounds into the food.

6 Next please. So, one example here is a  
7 kiln where barley after germination is being dried in  
8 a kiln. And also some specific browning reactions.  
9 And one can directly see whether the direct firing  
10 techniques with burners of above 1,100 degrees  
11 Celsius, they produce a lot of nitrogen oxides, and  
12 these are swept through the malt and of course  
13 interact then with constituents in the malt to form  
14 nitroso compounds, in other words to limit the  
15 temperature to degrees or to use indirect firing  
16 techniques or heating techniques that are very well  
17 established. Indirect heating techniques used  
18 throughout centuries that would remove that  
19 contamination quite efficiently.

20 Next slide. The main precursor for  
21 nitrosodimethylamine or NDMA in barley is gramine,  
22 again a compound that can easily be interacting with

1 nitrogen oxides by splitting off the nitrosamine  
2 elements. And as I said, the mitigation measures were  
3 quite effective to reduce the contamination to really  
4 very low levels nowadays.

5           Next, please. I think shows the  
6 estimated daily dietary intake of  
7 nitrosodimethylamine. And this is a collection that  
8 has been published by Hrudley up here in 2013, but the  
9 data are quite outdated I would say. So, there is not  
10 very much current data on nitrosamine contents in food  
11 nowadays. I think this is important for several  
12 reasons that we get updated data on this exposure for  
13 almost unavoidable food consumption of course, almost,  
14 but certainly unavoidable, almost unavoidable for the  
15 nitrosamine exposure that is connected to it. So, you  
16 see, this is all below 0.2 or 0.3, except for  
17 instance, for Australia. But as I said, I think we  
18 definitely need updated data on this exposure  
19 situation.

20           Next slide. So, now we turn to the  
21 endogenous formation thematics, and I start with  
22 mentioning the pioneers, not only for endogenous

1 formation but also for interaction of compounds with  
2 nitrosating agents. Sander and Burkle had already as  
3 early as 1969 made the first experiments to show that  
4 a secondary amine together with nitrite given to  
5 animals by gastric tube induces tumors that are  
6 indiscernible from the tumors of correspondent nitroso  
7 compounds. So, there is situ formation in the gastric  
8 compartment of nitroso compounds that is responsible.  
9 Then I have to mention Willie Lijinsky who had a  
10 tremendous amount of studies concerning the  
11 interaction of drugs with nitrous acid as a source of  
12 carcinogenic nitrosamines, incredible work and very  
13 important to revisit because in the face of our  
14 current situation. Finally, Richard Loepky is also a  
15 very important contributor because he has been mainly  
16 elucidating with formation of nitroso compounds from  
17 tertiary amines, also a very important piece of  
18 science that is published in many publications.

19 Next, please. When we consider  
20 endogenous formation, we need to take into  
21 consideration that we have already concerning the  
22 upper gastrointestinal nitrite, we have a situation of

1 circulation. As soon as you take up nitrite, for  
2 instance, by consuming nitrate-rich vegetables, then  
3 this process will go on, which is resorption from the  
4 gastrointestinal tract, and then that circulation, but  
5 then nitrate is resecreted through the salivary glands  
6 back into the mouth, the cavity of the mouth. The  
7 mouth has its own microbiome, and in that microbiome,  
8 there are microorganisms that are able to reduce the  
9 nitrate to nitrite. In other words, generates part at  
10 least of nitrosating agents by this way. There is  
11 about 25 percent of a given dose of nitrate that is  
12 recirculated, and about 6 percent of it that has been  
13 very well studied is reduced to nitrite. So, there is  
14 a potential already here. But that is not he only  
15 one. The other one as many of we know.

16 Next please. Because there is an  
17 interrelationship between nitrate, nitride, and  
18 nitrogen monoxide. The first point is that very  
19 researched by Steven Tannenbaum's group showing that  
20 humans produce daily about 50 mg of day for a 70 kg  
21 person, endogenous synthesis of nitrate that has been  
22 verified by input and output, and, of course, there is



1 a lot of variety of enzymes and proteins that can act  
2 as reductases and reduce nitrate via nitrites to  
3 nitrogen monoxide. There is further, of course, the  
4 function of nitrogen monoxide as a signaling molecule,  
5 which is generated from arginine and also creates a  
6 sustained source for nitrogen oxides and from that on,  
7 then also nitrite and nitride. And there is also a  
8 key component that is found in response to bacterial  
9 infections and during inflammatory reactions. Various  
10 publications address this. To give just a number for  
11 the dietary nitrate uptake, that is an average about  
12 175 mg per day as stated by EFSA (European Food Safety  
13 Agency) in 2008. This interrelationship of nitrates,  
14 nitrides, and nitrogen monoxide is again shown in  
15 the --

16 Next slide, please. These three  
17 components are metabolically interconvertible.  
18 Nitrogen monoxide can be oxidized to nitrate and  
19 nitride, and vice versa, nitrate and nitride can be  
20 reduced to nitrogen monoxide.

21 So, in summary, we have a certain  
22 endogenous physiological potential of generating

1 nitrogenous agents that is in part dependent on the  
2 nutritional exposure but is regulated and influenced  
3 by many other physiological parameters.

4           Next please. Of course, there have  
5 been estimates of endogenous formation of  
6 nitrosodimethylamine. I should perhaps mention before  
7 I go into that, that the urinary excretion of  
8 nitrosated amino acids has been used for a long time  
9 as an indicator, a biomarker for endogenous  
10 nitrosation in humans, and that is possible because  
11 these nitroso compounds are not mutagenic, not  
12 carcinogenic, and they are practically quantitatively  
13 excreted in the urine. So, they can be used as  
14 exposure biomarkers for nitrosation in vivo. And to  
15 go through carcinogenic nitroso compound, for  
16 instance, N-nitrosodimethylamine, this is very  
17 difficult because nitrosodimethylamine has a very  
18 short half-life in vivo. It is rapidly cleared from the  
19 body, maybe by cytochrome P450 metabolism. And  
20 therefore, attempts to measure this are sort of really  
21 difficult. And it is not only the difficulty itself  
22 you see, the data of these measurements are quite old,

1 1993 up to '86. Because there is another aspect,  
2 which is also important, and that is that in those  
3 early days, very often nitrosamine analysis has been  
4 plagued by the formation of artificial formation  
5 caused by artificial formation of nitroso compounds  
6 during workup and analysis. And if you see results in  
7 the literature that do not completely prove, for  
8 instance, by the addition of releasing the  
9 nitrosatable tracer compound that artificial formation  
10 of nitroso compounds is prohibited or inhibited, then  
11 these results are normally not really trustable.  
12 Anyway, if one takes these earlier results of very low  
13 levels of NDMA in blood samples that have been  
14 considered as reflecting steady state, then one would  
15 have incredibly high amounts of endogenous exposure to  
16 this compound. As you see here, it would be up to  
17 2,500 mcg per day or 1.4 to 35 mcg/kg per day. And if  
18 one bases this on a biomarker, the biomarker of  
19 alkylation of O6 oxygen of guanine that is also very  
20 well developed as a technique. Then, you would end up  
21 in a similar range of about 18 mcg/kg per day. I  
22 think these are important points to mention here and

1 to show that we really need definite, dependable  
2 confirmation and delegation of these results. I think  
3 it is very important to know more about this.

4 Next, please. Before we come to the  
5 last part of endogenous nitrosation considerations,  
6 just I would like to mention just shortly the WHO  
7 nitrosation assay procedure or short NAP assay that  
8 has been published very early already in 1980. This  
9 is a very simple chemical test under rugged conditions  
10 with relatively high concentrations showing the  
11 reactivity as is seen here on the left and on the  
12 righthand side of a couple of compounds that have been  
13 investigated by this test. You see that secondary  
14 amines of course are very high on the scale but also  
15 tertiary amines on the other side. And the problem  
16 with this test was that there were never cutoff levels  
17 of reactivity really defined scientifically. So, it  
18 has not been used very much.

19 Next, please. Human information of  
20 formation of nitroso compounds in humans is of course  
21 available. There are several publications on this  
22 one. One of several publications. This is one by

1 Tricker and Preussmann showing in patients with  
2 parasitic infections that piperazine is nitrosated  
3 endogenously, and it can be measured by urinary  
4 excretion of mainly mononitrosopiperazine, a little  
5 trace of binitroso and the corresponding metabolites.  
6 And the other compound mentioned is amidopyrine  
7 because it is an extremely reactive compound towards  
8 nitrosating agents, almost considered as a reagent to  
9 show the presence of nitrosating agents. And here, in  
10 this case, the in vivo nitrosation was measured in  
11 urine on simultaneous passage of some ethanol to  
12 inhibit cytochrome P450 clearance. And then it became  
13 available in the urine, nitrosodimethylamine could be  
14 measured.

15                   Next, please. So, the example of  
16 amidopyrine and its close analog, metamizole. The  
17 amidopyrine as I mentioned is extremely reactive and  
18 responding with the formation of dimethylnitrosamine,  
19 the other part of the panel. And this resulted very  
20 soon in withdrawal of amidopyrines from the market.  
21 And the analog here is metamizole. That is still on  
22 the market because it has been shown that the nitroso

1 compound that is shown, this mononitroso compound here  
2 shown in the green circle is nonmutagenic and  
3 noncarcinogenic. Again, close analogs showing vastly  
4 differing properties.

5           Next, please. Then, of course, you are  
6 all quite familiar with the occurrence of formation of  
7 dimethylnitrosamine in Sartans in the  
8 dimethylbiguanide (metformin) that is shown here. To  
9 my knowledge, at least, the source for the NDMA  
10 formation is not really elucidated yet. But this was,  
11 as I mentioned at the very beginning, the change with  
12 the Sartans, the change in the production process to a  
13 solvent, dimethylformamide, which of course then can  
14 react with nitrite that has been used to quench and  
15 destroy the azide that had been used to speed up the  
16 tetrazole ring. This then was the cause to form  
17 dimethylnitrosamine.

18           Next, please. That is similar for  
19 ranitidine, again structured as you may see here. The  
20 dimethyl amino group attached to the furan ring  
21 system. One could predict that this will carry  
22 easily. What I think is much more important is the

1 published study recently in 2016 with human volunteers  
2 where it was shown that enhanced levels of  
3 dimethylnitrosamine were excreted in the urine. And  
4 analytically, this was all right because these authors  
5 not only had the best sophisticated instruments,  
6 instruments with mass spectrometry to measure, but  
7 also, they were keen to shown that there is no  
8 artificial formation during analysis. So, from an  
9 analytical viewpoint, this is, in my opinion, all  
10 right. And again, this would be quite substantial,  
11 that is a nitrosamine formation rate that is going on  
12 as measured in humans. If it can be confirmed, in my  
13 opinion, it is very important to confirm, especially  
14 also raises the question why urinary excretion of  
15 dimethylnitrosamine is so relatively high because as  
16 we know, normally, it is very rapidly cleared and  
17 eliminated by metabolism.

18           So, we have one more, which is another  
19 H<sub>2</sub> receptor antagonist. Please, next slide. That was  
20 the first one to study cimetidine. That is the one  
21 here. That can also be easily nitrosated, but  
22 unexpectedly this compound, although it was mutagenic,

1 it was revealed not to be carcinogenic. And the group  
2 Magee has contributed a lot to show that the mechanism  
3 is that this compound is metabolically mainly  
4 denitrosated by glutathione and glutathione  
5 transferases by other SH groups of cystine or  
6 hemoglobin groups and even by cytochrome P450. And  
7 they also realize that the imidazole ring here may  
8 also be ionized, so this would also contribute under  
9 physiologic conditions to keep perhaps the  
10 nitrosatable ability or the biological effect of the  
11 nitroso compound. That is all I have to say. So, we  
12 come to the end.

13 Next, please. Most of you will know  
14 the group limits that have been defined recently based  
15 on the TD50 values of the original Gold Database, now  
16 the Lhasa Database that came to either lower default  
17 values, which are, you know, much lower than those  
18 that might be seen either by food exposure or even by  
19 endogenous exposure if these values can be confirmed.

20 Next, please. This should show the  
21 breakout. As I promised, I would like to contribute  
22 to show open questions, knowledge gaps, and research



1 needs. First to the exposure, I think it is very  
2 important to get a database update on the exogenous  
3 exposure. I think maybe from diet. Because it may be  
4 used as a suitable reference, correct, at least the  
5 suitability needs to be considered for risk assessment  
6 of other exposure pathways like contaminated drugs.  
7 And of course it is even more urgent to come to grips  
8 with the endogenous exposure and to develop validated  
9 analytical methodology to use PBBK-based estimates for  
10 human endogenous exposure and to check the  
11 productivity of the biomarkers of in-vivo formation.  
12 Are the nitrosamine acids also predicting carcinogenic  
13 nitroso compound formation are all important  
14 questions. And for the mitigation, the most important  
15 point, of course, is to scrutinize the technology and  
16 the processes for drug production to be sure that one  
17 can really mitigate interactions of potential  
18 nitrosating agents with APIs. But I think one should  
19 not totally leave out the possibility that given a  
20 pharmacological or toxicological tolerance of an API,  
21 that one can explore possibilities to replace critical  
22 structural elements as successfully achieved in other

1 areas. With these open questions, I leave you now,  
2 and thank you very much for your attention. Thank  
3 you.

4 MS. KING: Good morning. My name  
5 Sruthi King. I am one of the Associate Directors of  
6 Pharmacology and Toxicology in the Office of Generic  
7 Drugs in the Center for Drug Evaluation and Research.  
8 I'm one of the members of the Safety Team on the CDER  
9 Nitrosamine Task Force. We have been working together  
10 for the past 2-1/2 years, and as we head into the  
11 technical discussion today, my objective is to provide  
12 some context into the considerations and strategies  
13 used by FDA since the start of this incident and to  
14 highlight some of the ongoing challenges from the  
15 scientific and regulatory perspective.

16 Next slide, please. So, this is just  
17 to indicate that the views presented today are mine  
18 and do not reflect FDA policy.

19 Next slide, please. As you have just  
20 heard Dr. Eisenbrand present, he gave an excellent  
21 introduction to nitrosamines. We know that  
22 nitrosamines are present in food, water, tobacco,

1 multiple sources in our environment. We know that  
2 their chemistry is not new. Their toxicity and  
3 potency is not new. We know that there are potent  
4 rodent carcinogens, and some are probably human  
5 carcinogens. However, the presence of nitrosamines in  
6 drug products was alarming when we first became aware  
7 of it at the FDA in 2018. This contamination incident  
8 affected products globally, resulting in recalls of  
9 vital medications. And this required the development  
10 of highly sensitive analytical methods to detect and  
11 quantify these nitrosamines and investigate the root  
12 cause of formation of these compounds, so that we  
13 could identify appropriate control strategies.  
14 Managing this nitrosamine contamination incident in  
15 drug product has required multidisciplinary approaches  
16 to conduct the risk-benefit assessments, to  
17 collaborate with industry, and with our international  
18 regulatory partners, and to develop effective  
19 communication strategies so that our patients are  
20 aware of what is in their drug products.

21 Next slide, please. So, CDER (Office  
22 of Generic Drugs) became aware of the presence of

1 N-nitrosodimethylamine or NDMA in valsartan, which is  
2 one of the angiotensin II receptor blocker class of  
3 drugs. Since that time, we have learned that  
4 nitrosamines have been identified in active  
5 pharmaceutical ingredients or APIs, along with  
6 finished drug products. And this contamination of  
7 nitrosamines has been seen in generic drugs, as well  
8 as brand drugs, although the effect has been greater  
9 on generic drugs. Multiple nitrosamines have now been  
10 identified, and so we are looking into control  
11 strategies for single and multiple nitrosamines in a  
12 drug product. What you see on the righthand panel of  
13 this slide is some of the nitrosamines that FDA has  
14 identified in drug products and posted acceptable  
15 intake limits. Also included in this list is  
16 1-methyl-nitrosopiperazine and  
17 1-cyclopentyl-nitrosopiperazine, which have been  
18 identified in some anti-infectives. Despite the  
19 nearly 2-1/2 years into this contamination issue, we  
20 have still many ongoing challenges.

21 Next slide, please. So, what are some  
22 of the considerations that we make when we become

1 aware of the presence of a nitrosamine. We first look  
2 at whether it is a single or multiple nitrosamine. Is  
3 it a risk of formation, or are there actual levels  
4 being detected? Are the analytical methods being used  
5 sufficiently sensitive? And what is the root cause  
6 investigation tell us? Is this an API issue, or is  
7 this a drug product issue, or is it both? Once we are  
8 aware of what is the specific nitrosamine, we then  
9 consider what are the available nonclinical data to  
10 establish an acceptable intake. We then also consider  
11 what are the products that are being affected? What  
12 is the patient population that is being impacted by  
13 this contamination issue? Are these products  
14 medically necessary? What are the levels detected in  
15 the actual drug product, and how does this correspond  
16 to the acceptable intake of that nitrosamine? Should  
17 products be recalled, and if a recall is required,  
18 will this precipitate a drug shortage if there are no  
19 alternate options available. Therefore, there are  
20 multiple considerations that go into managing this  
21 issue and also to determine what is the appropriate  
22 next step.

1                   Next slide, please. This slide  
2 summarizes some of the key events and timeline of this  
3 incident from FDA standpoint. So, for each of the  
4 products that have been impacted by the nitrosamine  
5 contamination, FDA has conducted a risk assessment and  
6 posted acceptable intake limits, along with  
7 appropriate analytical methods for that nitrosamine  
8 and issued communications related to the risks of  
9 exposure, along with recalls that have happened, so  
10 that stakeholders are aware. As the incident evolved,  
11 FDA published a guidance in September of 2020 on the  
12 control of nitrosamines and drug products. We are  
13 actively engaged with our key stakeholders and  
14 researchers, along with our international regulatory  
15 colleagues to identify best approaches for risk  
16 assessments and control and mitigation strategies. As  
17 you can see, the incident began with contamination  
18 issue in antihypertensives in the ARBs, the  
19 angiotensin II receptor blocker drugs, and has now  
20 encompassed many classes of drugs, including  
21 ranitidine and nizatidine medications to manage  
22 diabetes and also infectious diseases such as

1 tuberculosis.

2                   Next slide, please. When FDA first  
3 became aware of this contamination issue, our Center  
4 Director at the time, Dr. Janet Woodcock, activated  
5 the CDER Nitrosamine Task Force to manage this  
6 incident. She foresaw the potential broad impact on  
7 the quality of medications and their impact on patient  
8 safety. The Nitrosamine Task Force is managed by the  
9 CDER Office of Counter-Terrorism and Emergency  
10 Coordination or CTECS. And this is a group that meets  
11 regularly. At any given time, there is over a hundred  
12 subject matter experts from across CDER and FDA that  
13 meet regularly to discuss and propose recommendations  
14 to mitigate the risk of nitrosamines in drug products  
15 and manage patient access to critical medications. As  
16 part of this effort, we routinely update senior  
17 management and discuss product and policy issues. We  
18 also engage international regulators to discuss  
19 harmonized approaches for addressing nitrosamine  
20 contamination on topics such as risk assessments,  
21 marketing actions, and sharing information related to  
22 these topics, along with communication strategies.

1                   Next slide, please. This slide shows  
2 the Multidisciplinary Coordination that has been  
3 happening in order to manage this nitrosamine  
4 incident. In the middle, you will see the CDER  
5 Nitrosamine Task Force, and they regularly engage  
6 various groups within FDA. And this kind of  
7 multidisciplinary coordination is necessary to manage  
8 this incident locally and engage with international  
9 regulatory partners to address this global issue. I  
10 will go into further detail on some of the  
11 interactions that happen in the coming slides. But to  
12 briefly highlight some of the key interactions, the  
13 Office of Pharmaceutical Quality, chemistry experts  
14 play a critical role in the root cause investigations  
15 and analytical method development, sample testing, and  
16 managing of applications and setting expectations for  
17 pre- and post-marketing issues. Depending on the  
18 nitrosamine that is identified, pharm tox experts  
19 within Office of Generic Drugs and Office of New Drugs  
20 are called upon to identify specific acceptable intake  
21 limits based on animal data. These acceptable limits  
22 are then used to develop methods and identify



1 analytical targets. Clinical experts also work  
2 closely with pharm tox and quality and identify  
3 appropriate maximum daily dose for the proposed  
4 product as the maximum daily dose is used to set  
5 control limits for specific products as some products  
6 may have multiple indications. Also closely involved  
7 is the Drug Shortage Staff. When medically necessary  
8 products are impacted, Drug Shortage Staff informs us  
9 about drug supply issues. There are also Compliance  
10 experts that are involved in inspections and recalls  
11 and also managing regulatory discretion issues along  
12 with regulatory policy, Regulatory Affairs Staff that  
13 respond to inquiries from citizens. We have had  
14 Congressional inquiries into this issue. There is  
15 Post Marketing Surveillance Staff that characterize  
16 risk of exposure from post-marketing data. And then  
17 finally, there is Communications Staff and Patient  
18 Engagement Staff, and we have had to develop a robust  
19 communication plan in order to communicate to patients  
20 and stakeholders on what is happening, how FDA is  
21 managing this issue. And lastly, FDA Researchers are  
22 also actively working on developing key specific

1 specialized methods for quality assessments, along  
2 with nonclinical information, and nonclinical methods  
3 to optimize study conditions.

4           Next slide, please. So, what are some  
5 of the complexities that we have had to deal with?  
6 Root cause investigations were critical to identify  
7 what is causing formation of nitrosamines, and this  
8 would help inform control strategies. We know that  
9 nitrosamines can be formed because of process-related  
10 issues with starting materials or the API itself,  
11 intermediates. There are supply chain issues that  
12 were identified where use of recycled or recovered  
13 materials was introducing contamination into the  
14 synthesis. There are also product stability issues  
15 where excipients in the formulation for example were  
16 contributing to the formation of these impurities.

17           Highly sensitive methodologies,  
18 analytical methods were necessary in order to identify  
19 and quantify these nitrosamines. Sample testing was  
20 necessary to identify which of the lots consisted of  
21 nitrosamines that were above acceptable intake, and  
22 this was used to inform recall decisions.

1 Unacceptable intakes and sensitive methods were  
2 necessary in order to set controls within the  
3 manufacturing process.

4           Lastly, we had to establish risk  
5 assessment expectations where nitrosamines in pending  
6 and approved products as there could be different  
7 considerations that were necessary. From a safety  
8 standpoint, we were aware that nitrosamines are part  
9 of the cohort of concerned group of compounds, and so  
10 they needed tighter control because they posed greater  
11 risk than other compounds. We know that lifetime  
12 exposure is calculated based on an increase in one  
13 case of cancer in 100,000 patients, and this was  
14 considered an acceptable level of risk. And so our  
15 task was to balance the risk of exposure to  
16 nitrosamine versus the risk of no access to medically  
17 necessary drug. We know that potency of nitrosamines  
18 varies across compounds. Some are mutagenic and  
19 carcinogenic, while others are not mutagenic but are  
20 still carcinogenic. Also, mothers are weakly  
21 carcinogenic. There is general agreement across  
22 regulatory bodies that nitrosamine should be avoided

1 or tightly controlled if they are unavoidable in drug  
2 products. When we were faced with various  
3 nitrosamines, we had to determine an acceptable level,  
4 and this was done using approaches in the ICH M7  
5 guidance, and this acceptable intake informed the  
6 analytical sensitivity of the methods that were  
7 necessary for detection of these compounds, along with  
8 informing recall decisions.

9           Next slide, please. So, how did we  
10 calculate acceptable intake? We had to identify a  
11 TD50, which is the dose that produces tumors in 50  
12 percent of the animals in a dosing group from an  
13 animal carcinogenicity study. As you have heard in  
14 Dr. Eisenbrand's talk, there is a wealth of  
15 carcinogenicity information for many of the  
16 nitrosamines. The acceptable intake is the daily dose  
17 of a nitrosamine when taken over a lifetime that  
18 represents a risk of one additional case of cancer in  
19 100,000 patients. How do we select the appropriate  
20 study when selecting a TD50. We look to see how  
21 robust the data are within the carcinogenicity study.  
22 And some of these criteria are listed here. How many

1 animals are there in a dosing group? What is the  
2 treatment regimen and dosing frequency? There are  
3 several nitrosamines with a number of studies that are  
4 available. Which is the appropriate study?  
5 Toxicology assessments and data presentation was  
6 another factor, along with relevance of the species  
7 and tumor. When establishing an acceptable intake,  
8 pharm tox experts in OGD, Office of Generic Drugs,  
9 worked closely with pharm tox experts in the Office of  
10 New Drugs. As I mentioned, generics and brand drugs  
11 were equally impacted by the nitrosamine issue, and  
12 therefore this collaboration was necessary to  
13 establish an acceptable intake.

14 Next slide, please. Not all  
15 nitrosamines have robust carcinogenicity data in the  
16 literature. Some nitroso compounds have no data at  
17 all. And so, in these cases, it was necessary to  
18 consider surrogate compounds to establish an  
19 acceptable intake. This is an approach that is  
20 described in ICH M7 where structurally or closely  
21 related structures could be used to justify an  
22 acceptable intake. When an appropriate surrogate is

1 not identified, we refer back to the acceptable  
2 intakes of NDMA, which is N-nitrosodimethylamine and  
3 N-nitrosodiethylamine to identify an appropriate,  
4 acceptable intake for the nitrosamine compound of  
5 interest. When we do have options for surrogates, we  
6 consider the robustness of the data that is available  
7 for that surrogate compound and structural  
8 similarities between that surrogate and the compound  
9 of interest. Just to note that some of the  
10 nitrosamines listed in the FDA Guidance have  
11 acceptable intakes that were developed using a similar  
12 process.

13           Next slide, please. What are some of  
14 the additional clinical complexities? A wide range of  
15 products have been affected, and this has impacted  
16 large numbers of patients with serious medical  
17 conditions, such as hypertension, diabetes, heartburn,  
18 tuberculosis. So, lack of medication, lack of  
19 medically necessary drugs could lead to public health  
20 emergencies, for example. So, the maximum daily dose  
21 is something that is necessary in order to calculate  
22 an acceptable intake or set control limits for a

1 specific drug product. And this is necessary to  
2 facilitate risk assessment of the manufacturing  
3 process. Another piece of this clinical risk-benefit  
4 assessment is a medical necessity evaluation. It is  
5 important to maintain patient access while balancing  
6 the risk of exposure to nitrosamines. And this  
7 multidisciplinary coordination goes into informing  
8 whether a product should be recalled. As I mentioned,  
9 prior to recall, there is a consideration of whether  
10 there are alternate therapeutic options for patients,  
11 whether the recalls will precipitate a drug shortage.  
12 And so, when there is a potential for drug shortage,  
13 additional strategies need to be considered.

14           Next slide, please. One of those  
15 strategies is the use of interim acceptable intakes.  
16 When patient access to drug is deemed medically  
17 necessary, FDA has applied flexibility by using  
18 interim acceptable intakes. Industry is a key partner  
19 in this short-term strategy as it offers flexibility  
20 to maintain patient access while process changes are  
21 instituted to remove or reduce nitrosamine formation.  
22 However, this requires multidisciplinary discussion

1 and consensus. Pharm tox staff along with clinical  
2 experts in Office of New Drugs and Office of Generic  
3 Drugs, Office of Pharmaceutical Quality, Drug Shortage  
4 Staff, Office of Compliance, and many others are  
5 needed in order to determine whether an interim  
6 acceptable intake can be tolerated to maintain patient  
7 access. This approach has been applied in several  
8 cases to mitigate drug shortages. For example,  
9 losartan was one of those cases where an interim  
10 acceptable intake was applied, along with rifampin and  
11 rifapentine.

12           Next slide, please. Not all products  
13 are used in the same way. Some are used as  
14 short-term, while others such as antihypertensives can  
15 be used long-term. So, how do we assess the risk of  
16 nitrosamines in short-term versus long-term use  
17 products. We know that M7 allows for adjustments  
18 based on duration of use for mutagenic impurities. We  
19 also know that nitrosamines are a cohort of concern  
20 compounds, and they are potent rodent carcinogens.  
21 Therefore, when assessing the risk of nitrosamines, we  
22 have considered lifetime exposure limits. And that is



1 because some nitrosamines have been shown to produce  
2 tumors at very short doses or even single doses, for  
3 instance. And therefore, there is uncertainty  
4 associated with a simple adjustment to the acceptable  
5 intake using the approach that is described in M7. In  
6 fact, M7 allows for this case-by-case approach where  
7 acceptable intakes for high-potency carcinogens, such  
8 as cohort of concern compounds, can be significantly  
9 lower than the typical less-than-lifetime adjustments.  
10 Therefore, the interim acceptable intakes do offer  
11 flexibility, but they are used as a short-term  
12 strategy to maintain patient access to medically  
13 necessary drugs. And this is a strategy we have used  
14 to avoid or mitigate a drug shortage. And adjustments  
15 based on duration of use have not been considered in  
16 determining the interim acceptable intake for a  
17 specific product.

18 Next slide, please. Another key factor  
19 or another key facet of the nitrosamine contamination  
20 issue in drug products from the FDA perspective has  
21 been our communication plan. Listed up here in the  
22 first bullet is the main FDA landing page for all

1 information associated or related to nitrosamines in  
2 medications. And using this hyperlink, you can access  
3 information that FDA has shared to inform industry of  
4 analytical methods of sampling and testing results and  
5 risk assessment strategies. This has been used to  
6 inform patients and care providers, pharmacy suppliers  
7 and distributors, list recalled products, and discuss  
8 alternate treatment options. FDA communications was  
9 critical to address media concerns and citizens  
10 petitions, along with Congressional inquiries. And  
11 finally, the Communication Staff is also actively  
12 engaged in talking with our regulatory partners  
13 internationally to discuss risk assessment strategies  
14 and harmonize on approaches on regulatory actions.

15 Next slide, please. One of the  
16 milestones in our communications strategy was the  
17 publication of the Nitrosamine Guidance, which you can  
18 access using the hyperlink that I provided in the  
19 first bullet. This Guidance provides detailed  
20 information on root cause assessments, regulatory  
21 expectations and risk assessments, and associated  
22 timelines, along with acceptable intakes for several

1 nitrosamines, and outlines risk mitigation strategies.  
2 It describes situations where there are single and  
3 multiple nitrosamines. Single nitrosamines may be  
4 allowed up to the compound-specific A1, and total  
5 nitrosamine exposure should not be exceeding 26.5  
6 nanograms per day. There have been several webinars  
7 hosted by the Office of Pharmaceutical Quality to  
8 describe this guidance in detail to industry. Since  
9 that time, as I have mentioned,  
10 methylnitrosopiperazine and  
11 cyclopentylnitrosopiperazine have been identified, and  
12 the acceptable intake for each is posted on the FDA's  
13 nitrosamine landing page.

14           Next slide, please. However, we have  
15 several challenges that remain. Root cause  
16 investigations have identified multiple factors that  
17 can contribute to nitrosamine formation. We know that  
18 stability of the formulation, the excipients used, and  
19 storage conditions are some of the factors that can  
20 contribute to nitrosamine formation. Some of these  
21 factors can have broad impact on many classes of drugs  
22 because of their history of use in drug development.

1 The risk assessment is the key to understand whether  
2 nitrosamines can be completely eliminated or if  
3 control or monitoring are better options. In addition  
4 to working with firms that submit their risk  
5 assessments, FDA is proactively reaching out to firms  
6 with manufacturing processes that pose risk of  
7 formation of nitrosamines. The goal is to ensure that  
8 there is high quality and safe drug supply in the U.S.  
9 market. As new and more sensitive methods are  
10 developed, there is also increasing awareness of the  
11 presence of API-related nitroso impurities. These  
12 previously unidentified compounds, uncharacterized  
13 compounds, pose a unique challenge when it comes to  
14 risk assessments, and appropriate control strategies.  
15 Additionally, there is an effort to harmonize with our  
16 regulatory partners on analytical methods for testing,  
17 and to further discuss method sensitivity, monitoring,  
18 and other related topics.

19 Next slide, please. From a safety  
20 standpoint, it is important to acknowledge that  
21 nitrosamines are in our food, in our water, and can be  
22 formed endogenously. And so, we have to consider how

1 this exposure to nitrosamines from other sources,  
2 including endogenous production, how this compares to  
3 exposure from drug products. How does this impact our  
4 risk assessments and proposed control strategies for  
5 nitrosamines in drug products. In some cases, the  
6 quantity and quality of data available varies for  
7 nitrosamines. If data are not robust, identification  
8 of an appropriate TD50 to calculate an acceptable  
9 intake is challenging. We are becoming increasingly  
10 aware that improved testing methods are identifying  
11 previously uncharacterized nitroso impurities that  
12 have no published safety data. So, how do we balance  
13 this risk of exposure to nitrosamine while maintaining  
14 a high-quality drug product that is safe and effective  
15 for its indicated use for the American public. We are  
16 using surrogate compounds for assessment, but they  
17 come with their own limitations. Of those surrogates,  
18 it is important to identify compounds with robust  
19 carci data. We do apply chemical informatics  
20 approaches to inform potency. We look at structural  
21 similarity, metabolic activation. Some of these  
22 nitroso impurities are bulky, and considerations of

1 how size and steric hindrance impacts their potency is  
2 another challenge.

3           Next slide, please. So, as we head  
4 into the workshop today, we have to look back and say  
5 over the past 2-1/2 years, we have certainly learned a  
6 lot; however, I have described some of the challenges  
7 that are still ongoing. FDA researchers play a key  
8 role in optimizing testing conditions for nitrosamine  
9 safety assessments. We have researchers who are  
10 working on nonclinical safety assessments to best  
11 characterize mutagenicity and carcinogenic risk of  
12 some of these nitrosamine compounds. In particular,  
13 it is important to develop a testing paradigm for  
14 those that have little to no published data for those  
15 impurities that are previously unidentified or  
16 uncharacterized. What are some of the key pieces that  
17 are necessary to identify an acceptable intake?  
18 Bridging this gap in information also requires  
19 collaboration with experts in academia and industry,  
20 along with our international regulatory partners to  
21 identify harmonized risk assessment strategies. This  
22 concludes my presentation.

1                   Next slide, please. I look forward to  
2 the discussion over the next two days amongst our  
3 panel of experts. I want to thank you for your  
4 attention, and I would like to acknowledge the  
5 colleagues on the Safety Team, Drs. Dorsam, Atrakchi,  
6 McGovern, and Karen Davis Bruno. And also the members  
7 of the CTECS Nitrosamine Task Force, various  
8 colleagues from CTECS, our OPQ colleagues, Office of  
9 Generic Drugs and New Drugs, Drug Shortage Staff,  
10 Office of Communication and Compliance. We have all  
11 worked very closely together over the last 2-1/2  
12 years. So, thank you for your attention, and I look  
13 forward to an exciting workshop. Thank you.

14                   DR. ATRAKCHI: Thank you, Dr.  
15 Eisenbrand and Dr. King for the comprehensive and  
16 information presentations. We now begin with the  
17 questions. They are organized under two headings,  
18 exposure and risk assessment and chemistry. They  
19 focus on important issues and the challenges of  
20 impurities in medicines in general and nitrosamines in  
21 particular. We are also interested as you have heard  
22 in the panel's thoughts on the research needed to

1 further our understanding of nitrosamines. We begin  
2 with the first question under the heading of exposure  
3 and risk assessment.

4           What are the endogenous levels of  
5 nitrosamine formation in humans and rodents? Once  
6 formed, what is the rate or kinetics of elimination?  
7 What are the conversion rates in the liver,  
8 circulation levels in the blood, and normal  
9 variations? If this information is not available, can  
10 it be determined experimentally?

11           As we know and we have heard from Dr.  
12 Eisenbrand, nitrosamines are present in the  
13 environment. We also know, not only are we exposed to  
14 them exogenously, but they are also formed  
15 endogenously. Therefore, it is imperative that we  
16 understand their pharmacokinetics in order to  
17 determine exposure and ultimately calculate risk.  
18 This question asked how much do we know about  
19 nitrosamine absorption, their distribution, how  
20 quickly they are metabolized, and how fast they are  
21 excreted. I would like to start by asking Dr. Hecht  
22 to begin the discussion.



1 DR. HECHT: Yes, so, we know quite a  
2 bit about endogenous formation based on studies that  
3 have been carried out with nitrosoproline where  
4 subjects have been dosed with proline plus nitrite or  
5 even proline plus nitrate, and then nitrosoproline can  
6 be quantified in the urine because nitrosoproline is  
7 not metabolized. It is also not carcinogenic. So,  
8 many studies on nitrosoproline formation have been  
9 carried out, which demonstrate the endogenous  
10 formation of nitrosamine. So, the overall yield is  
11 actually quite low based on the amounts of proline and  
12 nitrate that are given. But we do not have reliable  
13 data for compounds such as dimethylnitrosamine because  
14 dimethylnitrosamine is rapidly metabolized in the  
15 liver, and we do not have good data on the  
16 quantitative formation and excretion of its  
17 metabolites. One can visualize why this could be  
18 addressed, but it is very challenging. So, while,  
19 from a structural activity point of view, you would  
20 expect some endogenous formation of  
21 dimethylnitrosamine from dimethylamine, for example,  
22 in the diet and nitrate and nitrite that are normally

1 taken in. But quantitatively, we do not have good  
2 data because of its rapid metabolism. So, it is still  
3 a challenge to determine whether the endogenous  
4 formation of carcinogenic nitrosamine, such as  
5 dimethylnitrosamine would be far greater, for example,  
6 than the exposure from pharmaceuticals. That is my  
7 answer.

8 DR. ATRAKCHI: Next we go to Dr.  
9 Kyrtopoulos.

10 DR. KYRTOPOULOS: Thank you. And  
11 generally I agree with what Dr. Hecht has just said.  
12 And he mentions that Dr. Eisenbrand that basically  
13 three approaches have been used to try and estimate,  
14 basically guess, and the formation for  
15 dimethylnitrosamine. This is really the only  
16 carcinogenic nitrosamine about which we can try to  
17 guess regarding its endogenous formation. Based on  
18 the concentrations of NDMA that have been found in  
19 blood or in urine and some estimates of the  
20 toxicokinetics of NDMA and having in mind that it is a  
21 very small fraction of NDMA that is actually excreted  
22 in the urine, people have tried to come up, and they

1 have come up with estimates as we have previously of  
2 hundreds to thousands of micrograms of total  
3 throughput of NDMA through endogenous formation. I  
4 can say a little bit more about the third approach  
5 towards the same question. Based on the fact that  
6 NDMA methylates DNA, it gives rise to methylated  
7 adducts, and it is possible to measure methylated DNA  
8 adducts in human patients. Of course, there is a  
9 question of what is the source of these adducts, but  
10 assuming that NDMA is a major source, one can try to  
11 use animal data and extrapolate back to how much  
12 exposure would be required to give rise to the adducts  
13 we know. So, I would like to just take you through  
14 this argument. Data on methylated DNA adducts in  
15 humans are really quite limited, and most of them have  
16 been based on small pilot studies. However, there is  
17 a series of studies that we had carried out some years  
18 ago, which were relatively extensive. We have  
19 measured O-6 methylguanine, which is an important DNA  
20 adduct, premutagenic and precarcinogenic, this one by  
21 NDMA, and we had measured it in human blood DNA, that  
22 is in blood leukocytes. And I would like to show you

1 some numbers because I think it is important to have  
2 an idea of the scale of what we find.

3           If I could have the next slide, please.  
4 In three studies all together, which we carried out  
5 over a period of 10 years or so, we looked at about a  
6 thousand blood samples from women citing general  
7 environmental exposure. In about 700 of those  
8 samples, we could measure 0-6 methylguanine, and we  
9 had an average content of 16 attomoles per microgram  
10 DNA. An attomole is  $10^{-18}$  moles. With a  
11 range of 4.5 to 109. Sixteen attomoles corresponds to  
12 27 moles per  $10^{-8}$  moles of guanine or about  
13 59 or 60 molecules per diploid cell. I would like to  
14 explain why I use these units of content per cell.  
15 This is because repair of adducts is an issue that  
16 comes up frequently in discussing response and risk  
17 assessment. And it may come up during the discussion  
18 of subsequent questions. 0-6 methylguanine is  
19 repaired by a protein, a methyltransferase, known as  
20 MGMT which acts stoichiometrically for every molecule  
21 of adduct that it repairs, a molecule of  
22 alkytransferase is destroyed. That means that if

1 there are enough adducts in the cell to be repaired,  
2 and if MGMT does get depleted, that means that the  
3 dose response curve might show an upward turn. So,  
4 expressing the adducts on the basis of cellular  
5 content allows us to compare them with the content of  
6 MGMT in differing cells. Now, in experimental animals  
7 treated with low oral doses of dimethylnitrosamine  
8 (NDMA), blood DNA accumulates more adducts than almost  
9 all other tissues expect for the liver, which  
10 accumulates a little bit more adducts. So, if the  
11 adducts that we measure do come from NDMA, these  
12 levels are unlikely to be exceeded by other tissues.  
13 In other words, what we measure in blood represents  
14 the higher level of adducts in any tissue. As far as  
15 I am aware, MGMT content of primary human tissues is  
16 substantially some orders of magnitude higher than the  
17 highest adduct levels we have seen in human blood DNA.  
18 In other words, the 109 attomoles per microgram DNA is  
19 much, much lower from 10 to 100 hundred times than the  
20 levels of MGMT that are usually found in human  
21 tissues. So, that means that it is unlikely that loss  
22 of repair is likely to play a role in environmentally

1 relevant exposure levels.

2                   Now, how likely is it that these others  
3 come from NDMA. We know about a dozen methylating  
4 agents -- experimental, industrial, medicinal, of  
5 endogenous origin to which humans may be exposed.  
6 From studies in rodents, we know that NDMA is by far  
7 the most efficient chemical capable of giving rise to  
8 O6-methylguanine in blood leukocytes in-vivo.  
9 Therefore, taking into account the degree of human  
10 exposure to these chemicals, I think it is not  
11 unreasonable to think that NDMA is probably the most  
12 likely source of these adducts in the human tissues  
13 that we measure. So, assuming that this is so, we can  
14 attempt to estimate the exposure that is required to  
15 give rise to the others that we see based on those  
16 responses in animals. There have been many  
17 stoichiometric studies published at times. Many of  
18 the older studies have used quite high doses of  
19 methylating agents, NDMA in particular, which likely  
20 decreased from MGMT. We have carried out studies  
21 using much lower levels of NDMA, non-MGMT depleting,  
22 and so we have those response information, primarily

1 in rodents but also in monkeys, in patas monkeys.  
2 What we have found that if the dose of NDMA is  
3 expressed not as an amount per kilogram for the weight  
4 but as amount per square meter surface area, and if  
5 those response curves for adduct accumulation in blood  
6 DNA in different species become quite compatible, well  
7 within -- the slopes are within a factor of 5 easily.  
8 And I should add that we have also found that the rate  
9 of repair of O6-methylguanine in blood leukocytes is  
10 similar in rats, in monkeys, and also in humans who  
11 have been treated with methylating drugs. So, if we  
12 can go to the exposure response curves.

13 Can we see the next slide, please. On  
14 the left, you can see the adduct accumulation curves  
15 in blood DNA of rats treated chronically with NDMA in  
16 the drinking water, and on the right, you see the dose  
17 response curve for the steady state levels, which is  
18 fairly linear. The dashed horizontal line corresponds  
19 to the upper limits of adducts measured in humans, and  
20 from that, we can see that the corresponding exposure  
21 is just under 500 micrograms per square meter, which  
22 adjusting, extrapolating to the human exposure would

1 correspond to 982 micrograms per day. That is for the  
2 maximal adduct levels, and for the mean adduct levels,  
3 something around 144 micrograms. So, we are speaking  
4 again about background NDMA exposures of hundreds of  
5 micrograms per day, which are much higher than those  
6 that are derived from external exposures. And  
7 therefore, they are likely to be of endogenous origin.  
8 And, of course, these numbers are in the same ballpark  
9 as those presented earlier by Dr. Eisenbrand, coming  
10 from the Hrudley publication of 2013. For some  
11 reason, they had used our data to come up with other  
12 higher numbers. In any case, this is where we stand.  
13 Just two words about the uncertainties of this  
14 analysis. First, I liked Dr. Eisenbrand's statement  
15 about the need to validate the measurements. And we  
16 used immunochemical methodologies, and the  
17 immunochemical methodologies when pushed at their  
18 limit of sensitivity always had question marks. We  
19 had taken steps to minimize these question marks, but  
20 one would like to see measurements of DNA adducts  
21 carried out by more reliable modern methodologies,  
22 analytical methodologies. Secondly, we are not really



1 sure about the similarity of the dose response curves  
2 in humans with those of the rats that we have used.  
3 And perhaps an important thing to also have in mind is  
4 that we really do not understand the determinants of  
5 the endogenous formation of NDMA. No known studies  
6 have really been carried out to answer this question.

7 And I stop there. Thank you.

8 DR. ATRAKCHI: Thank you. Now, we move  
9 to Dr. Rice.

10 DR. RICE: First, I want to thank Drs.  
11 Eisenbrand, Hecht, and Kyrtopoulos for their  
12 comprehensive overviews of some of the issues  
13 associated with endogenous levels of NDMA and other  
14 nitrosamine formation. And I cannot add a great deal  
15 to what they have already presented. I should just  
16 like to draw attention to the fact that NDMA and other  
17 nitrosamines largely are metabolized by P450-2B1, and  
18 that metabolism is subject to competitive inhibition  
19 by simultaneous administration of other substrates for  
20 that enzyme. Dr. Kyrtopoulos especially has done a  
21 lot of work with ethanol consumption concomitantly  
22 with the administration of nitrosamine in experimental

1 animal and better suited perhaps, so I can raise this  
2 issue. But the basic point is that the distribution,  
3 excretion, and so forth is not something that is  
4 unchanging but is very dependent on what other  
5 exposures are simultaneously occurring. But great  
6 shifts both in organ distribution of methylating  
7 effects, as well as excretion of nitrosamines can  
8 occur when substances compete for p450 simultaneously  
9 in my experience. Consequently, I would just note the  
10 need to keep in mind in efforts to understand the  
11 levels and adducts of elimination such that it is very  
12 much dependent on what else is present in an  
13 individual. Thank you.

14 DR. ATRAKCHI: Thank you. Dr.  
15 Eisenbrand. I know you have spoken quite a bit, but  
16 maybe you can add a little bit more.

17 MR. EISENBRAND: No, I would like to  
18 actually. Thank you very much. I think this  
19 Question 1 is one of the most important questions of  
20 the whole meeting here because I think we really need  
21 to get reliable information about endogenous exposure,  
22 especially to dimethylnitrosamine but not exclusively.

1 There are other compounds as well as Dr. Shukars [ph],  
2 and some have shown a couple of years ago.  
3 Methylation is also carboxymethylation and some  
4 others. So, as I proposed at the end of my talk, we  
5 really need to revisit this endogenous formation and  
6 exposure question quite a bit. I think it is very  
7 important also to put in relation what happens by  
8 potential exposure to drug constituents. And it is  
9 not only that, but the second point is also as I  
10 mentioned in my talk as well that we also need an  
11 updated database on exposure from food to compare with  
12 potential exposure from drugs. I mean, if you look  
13 into the proposed AI levels, the acceptable intake  
14 levels, these are maybe from the TD50 values. Some of  
15 them have a good database and data density but most of  
16 them not. And in my opinion, we end up with a series  
17 of theoretical values in the nanogram range, which is  
18 all right, of course, as a safety measure, but we need  
19 also to have this view of what happens in real life,  
20 and that is my meaning as a toxicologist. We need to  
21 know what we are normally exposed to, not only  
22 exogenously maybe by our nutrition but also by the

1 endogenous exposure. Nowadays, we have the means to  
2 measure that. It is not the situation of 30 years or  
3 50 years ago. And as Dr. Kyrtopoulos pointed out, I  
4 think one biomarker that is already very well usable,  
5 that is 06-methylguanine. And again, we have to have  
6 the adequate PBPK random models and come to numbers  
7 that are really dependable. I think it is very  
8 important.

9 DR. ATRAKCHI: Thank you. And Dr.  
10 Bucher.

11 DR. BUCHER: Yes. I agree that the  
12 improved methodologies have improved data for  
13 endogenously generated nitrosamines and are very good  
14 and very useful in this context. I am somewhat afraid  
15 that it is going to take quite a while to generate  
16 this information and to be able to actually contribute  
17 to this discussion. I think it is going to be perhaps  
18 necessary to make some other considerations that I  
19 think will be coming out in the discussions to some of  
20 the other questions later on. So, I would hope that  
21 we would keep experimental work going in this area or  
22 restart experimental work in this area. I think there

1 are some practical issues related to the timing of  
2 generating data to answer the questions that are  
3 really, really on the table at the moment. Thank you.

4 DR. ATRAKCHI: Thank you. And Dr.  
5 Zeiger.

6 DR. ZEIGER: Thank you. I think the  
7 earlier speakers have pretty much covered all the  
8 points pretty well. One additional item I would like  
9 to interject is whenever we do these types of studies,  
10 we assume that the kinetics and the potency of the  
11 mutagenic or carcinogenic response will be similar in  
12 humans and in the test rodents. And we know at least  
13 from mutagenicity studies that there is quite a bit of  
14 difference in the rate of activation by liver of these  
15 various nitrosamines and differs quite widely just  
16 between mice and rats and hamsters where we have data.  
17 We have no idea how those measurements would translate  
18 to a human exposure in a human situation. I just  
19 wanted to raise that point now. But other than that,  
20 I have nothing to add.

21 DR. ATRAKCHI: Thank you. Very good  
22 points. And Dr. Adamson.

1 DR. ADAMSON: I think the talks by Dr.  
2 Eisenbrand and Dr. King were very helpful, but I think  
3 the additional comments that Dr. Eisenbrand made are  
4 particularly important because the endogenous  
5 formation from both the data and the literature and  
6 what Dr. Kyrtopoulos presented shows magnitudes of  
7 formation of endogenous nitrosamine, particularly DMNA  
8 much higher than we are getting in the medicines in  
9 which it has been detected. So, I think with the  
10 newer techniques, analytical techniques need to be  
11 applied to both endogenous formation and particularly  
12 also with food. Because the amount in food varies  
13 from country to country with the current analytical  
14 techniques and also varies between various  
15 investigators. So, I think using the new analytical  
16 techniques should help us because at the present time,  
17 the endogenous formation of nitrosamines and the  
18 amount in food overwhelms what has been found in the  
19 medicines to date. So, I would emphasize that what  
20 Dr. Eisenbrand said, we need to go back and look at  
21 food and endogenous formation with the newer  
22 analytical techniques. Thank you.

1 DR. ATRAKCHI: Thank you. And Dr.  
2 DiNovi.

3 DR. DINOVI: I don't actually have much  
4 to add, but based on what we just heard there, I would  
5 agree. It does appear as though the endogenous  
6 exposure is going to overwhelm the food. There are  
7 differences from country to country, but it is  
8 comforting that if you look at the surveys that have  
9 been done -- and I'll talk a little bit about this  
10 this afternoon probably -- they are relatively  
11 similarly, and the role in that sub 1 microgram a day  
12 range, endogenous will have to be considered further.  
13 Thank you.

14 DR. ATRAKCHI: Thank you. I think we  
15 will discuss this a little bit later on with the other  
16 questions. But one issue that to me seems very  
17 important is we need to have analytical methods that  
18 can distinguish between endogenous and exogenous  
19 formation. Otherwise, the data will not be very  
20 accurate. With that, I would like to move on to the  
21 second question.

22 Can nitrosamines be classified? If

1 yes, what is the basis of their classification? Could  
2 they be classified based on carcinogenic potency, on  
3 their chemical structure, on the chemical reactivity,  
4 direct alkylating agents versus those that require  
5 metabolism, or based on the adducts that are formed as  
6 just heard, the O6 or the N7 methylation? Any other  
7 basis for classification? And once we choose a  
8 classification, what is the basis of using that over  
9 the other ones? If classification is not possible, is  
10 it feasible to calculate a single, acceptable intake  
11 value for nitrosamines? That is we can come up with a  
12 class-specific limit using the existing  
13 carcinogenicity study results of over 100 nitrosamines  
14 irrespective of the study quality. It seems that the  
15 main concerns for pharmaceuticals and maybe  
16 biopharmaceuticals are the volatile nitrosamines in  
17 particular. As noted earlier, since the discovery of  
18 the toxicities of these nitrosamines, much of the  
19 carcinogen assessment studies were done in the '70s  
20 through the '80s and early '90s by scientists here in  
21 the U.S., as well as abroad, some of whom are as we  
22 already noted are here with us today on the expert



1 panels. Nitrosamines were shown to be toxic, both in  
2 androgens and carcinogens. They are also teratogens.  
3 They have a wide range of potency on order of  
4 magnitudes, and the majority cause cancer in around 40  
5 animal species. They cause tumors in multiple organs,  
6 different durations of exposure, some would induce  
7 tumors after a single dose even though their half-life  
8 is short within a few hours.

9           They also have different latency. All  
10 of this makes classification of nitrosamines that are  
11 quite a bit difficult. However, it is an important  
12 and critical aspect of what we are trying to discuss  
13 today at this workshop. And with that, I'd like to  
14 start with Dr. Eisenbrand.

15           DR. EISENBRAND: Thank you, Dr.  
16 Atrakchi. Again, a very important question is going  
17 to the classification of nitroso compounds. Of  
18 course, one can use a classification based on trying  
19 to develop a system for carcinogenic potency and  
20 rating, and of course, that has been carried out  
21 before already, based mainly on the TD50 values that  
22 are in the former Gold database and the CPDB. And it

1 is a way of doing that. Probably at the moment, it  
2 may be the best way to go on until further questions  
3 have been addressed sufficiently such as the ones we  
4 have just discussed before. It is the relation  
5 between the drug-mediated exposure to the exposure  
6 that is coming from food unavoidable or from  
7 endogenous exposure. And I agree that this may need  
8 some time to systematically do the research that we  
9 can depend on and for that time being, it may be the  
10 best way to go just with the deferred proposals of  
11 group-specific values concerning the acceptable  
12 intakes based on the TD50 procedure. So, this is a  
13 way to go. And the second point, of course, it is a  
14 complex task, but it can be simplified because we know  
15 already about defined chemical structures that inhibit  
16 carcinogenesis or mutagenesis. As we have heard,  
17 these are the tertiary butyl groups, and these are the  
18 ionic compounds like the nitrosated amino acids. And  
19 on the other side, there might be also protonation  
20 that is important to reduce bioavailability. So,  
21 there are possibilities to look into this with more  
22 defined questions to answer.

1           The chemical reactivity of course that  
2           would be the first thing to consider, that  
3           nitrosoureas for instance or carbamates or this other  
4           compounds that do not require metabolic activation,  
5           they react by themselves, and this is a consideration  
6           that is also important when you consider stability  
7           questions. For instance, I would personally think  
8           that nitrosoureas are not really very stable, so it  
9           might be that there comes stability issues into  
10          consideration showing that within a certain time of  
11          let us say storage of so, these compounds may be done.  
12          Of course, this is open to research. It has to be  
13          really looked into quite closely. But just as a  
14          potential point of view. And what I would personally  
15          think is very promising is to use the biomarkers of  
16          epilation. 06 methylation or carboxymethylation or  
17          some others, I think that is a good way to go, and it  
18          should be really substantiated by I would say PBBK  
19          modeling of the enzyme activity that is going on and  
20          formation and repair and all these things. I think we  
21          are much better today to address these questions in a  
22          reliable way. So, that could also be a good

1 possibility.

2           In terms of other I do not have very  
3 much further to add, and the classification I may just  
4 recall you that EFSA (European Food Safety Agency) has  
5 proposed a couple of years ago the margin of exposure  
6 methodology where you use a benchmark dose as obtained  
7 in animals, mostly on the low side of the dose  
8 response score, at least not more than 10 percent  
9 population percentage of the dose effect or even  
10 lower. And do that with the appropriate modern  
11 methods of modeling. And then if you have this BNDL  
12 value or BNDL 10 or BNDL 5 or around that area or even  
13 lower, then to use for risk assessment the distance to  
14 human exposure. And of course, again, we come back to  
15 human exposure, but this human exposure I think has  
16 considered overall exposure, the real-life exposure.  
17 And then determine the margin of exposure between this  
18 BNDL value and the exposure of the consumer nowadays  
19 on average. That I think I would think is a good way  
20 to good. EFSA has tentatively said that if this  
21 margin is more than 10,000, the space between the BNDL  
22 value and the consumer's exposure, then one could say

1 that is of very low concern, no primary concern. And  
2 I think it is a way of addressing these things. My  
3 idea would be that this is also a good way to go. So,  
4 I stop here. Thank you very much.

5 MS. ATRAKCHI: Thank you. Dr. Bucher.

6 DR. BUCHER: So, to me the key to this  
7 question is can nitrosamines be classified. Whether  
8 they should be classified or not, under certain  
9 conditions, that is another discussion. But to the  
10 question of can they be classified, I would agree that  
11 there is a qualifying yes. Chemical-structured-based  
12 models have been published, and do a reasonable job of  
13 classifying nitrosamines as carcinogenic or not. A  
14 few models have attempted to classify nitrosamines  
15 according to their carcinogenic potency using the TD50  
16 values as described earlier. And while I agree that  
17 the benchmark dose calculations and the margin of  
18 exposure models are better than the TD50s, given what  
19 we have to work with, I think the TD50s are going to  
20 have to remain as part of our considerations.  
21 Nitrosamines have also been classified by quantitative  
22 structure activity, relationships using structural

1 alerts for carcinogenicity with some success, and of  
2 course, expert judgement and additional  
3 experimentation is also valuable and needed and will  
4 need to be used along with modeled results to improve  
5 the predictivity of these models. Many of the  
6 nitrosamines that have been identified as contaminants  
7 in drugs require metabolic activation, so such things  
8 as susceptibility to P450 hydroxylation in the alpha  
9 carbon. And also important is the half-life of the  
10 resulting diazonium ion and reactivity of the  
11 carbynium ion. All of these things are very important  
12 to consider with respect to expert judgement, and  
13 including in new models. To widely use these  
14 parameters, they would need to be predicted in many  
15 cases, so this would reduce the confidence of the  
16 outcomes of some of the models. So, to me, there are  
17 a variety of classification modeling approaches that  
18 could be and have been applied to this question. But  
19 so far, even the best of the models are only pretty  
20 good. They are very far from perfect, and some are  
21 fairly computationally intensive. As to which model,  
22 I would choose for FDA going forward in the absence of

1 anything better, I would choose one of the reasonably  
2 predictive QSAR models and incorporate carcinogenic  
3 potency using the TD50 values and measured with a  
4 heavy dose of expert judgment.

5           Turning to the question of the  
6 feasibility of a single acceptable intake, I believe  
7 this is possible. Again, and relying on the  
8 carcinogenic potency database. If one simply scans  
9 the estimated TD50 values for the over 100-plus rodent  
10 carcinogens for nitrosamines in the database, they can  
11 reasonably be placed within some ranges. In a few  
12 potent rodent carcinogens with a lifetime daily TD50  
13 doses below 1 mg/kg, many of these have values between  
14 1 and 10 mg/kg per day and others between 10 and 100  
15 or even higher. Those with a very high TD50s can  
16 probably be ignored insofar as human hazards from drug  
17 contamination is concerned, and acceptable intakes  
18 could be calculated for substances falling within  
19 these high potency ranges. And it seems reasonable to  
20 use the European Medicine Agency's proposed linear  
21 dose extrapolation based on either the most potent or  
22 the median nitrosamine potency in the range to the

1 risk level of 1 in a 100,000 as proposed in the AMA  
2 report. Actual TD50 values or modeled estimates could  
3 also be used, but you should recall, of course, as  
4 pointed out earlier, the potency estimates from the  
5 rodent cancer studies are very imprecise. They depend  
6 on a whole list of factors having to do with the study  
7 design and the power to detect increases in tumors, to  
8 study at length of the extent of histopathologic  
9 evaluation in these studies, and other factors related  
10 to the way the study was performed. With that said, I  
11 think the data probably have value in predicting  
12 relative carcinogenic potency and perhaps if used  
13 within these various ranges of TD50s that I've  
14 mentioned, they may be useful, and clearly, they have  
15 already been incorporated into some of the existing  
16 published models of nitrosamine carcinogenicity. I  
17 think I'll stop there.

18 DR. ATRAKCHI: Thank you. And Dr.  
19 Guttenplan.

20 DR. GUTTENPLAN: I don't have too much  
21 to add. I just have the feeling that we need to have  
22 some way of superimposing the difference between human



1 metabolic activation of carcinogens and the rodent  
2 data. I am not sure the best way to do that but maybe  
3 with some model compounds, at least, it would be  
4 possible from what we know about human data to compare  
5 it to rodent data. And maybe there is some way of  
6 adjusting the carcinogenicity from rodent values into  
7 human values, possibly by looking at their ability to  
8 form say O6-methylguanine if you have a carcinogen in  
9 rodents that is very good at forming it, and it is not  
10 so good in humans it would suggest that there are  
11 metabolic differences or pharmacological differences  
12 that might account for these differences. So, I would  
13 say the carcinogenic potency is the first stage, and  
14 it is probably the best we have at the moment. But I  
15 would suggest that there are improvements that could  
16 be made. And that is about all I have to say on the  
17 issue.

18 DR. ATRAKCHI: Thank you. Dr. Zeiger.

19 DR. ZEIGER: Right now what we use is  
20 primarily mutagenicity versus non-mutagenicity, which  
21 is at first the Ames test, which is the first test  
22 generally applied to these chemicals. And obviously,

1 the ones that are mutagenic are presumed to be  
2 carcinogenic. You know, unfortunately, as I have  
3 mentioned, I think I mentioned before, the mutagenic  
4 potency does not correspond to the potential  
5 carcinogenic potency with these chemicals. We have in  
6 the Ames test a mutagenic potency range of about four  
7 or five orders of magnitude, but whether these compare  
8 with carcinogenic potency, they generally do not. We  
9 heard before that, for example, nitrosodiethylamine  
10 has a higher carcinogenic potency than the diethyl  
11 form. But in the mutagenicity studies, they have  
12 equivalent potencies. So, that does not help. I  
13 think what we really need, and it has been addressed  
14 before, is that we need to have more information on  
15 the human metabolism of these substances. We do not  
16 have very much on in-vitro human metabolism using  
17 either metabolic incompetent cells or just liver  
18 homogenates. Without this information to compare it  
19 to the rodent information, I am not sure if we can go  
20 much further than going through just like basing it on  
21 structure, basing it on DNA alkylation. Whether it is  
22 possible to calculate a single acceptable intake, I do

1 not think we have enough information to even address  
2 that question at this point. And that is all I have  
3 to say at this point.

4 DR. ATRAKCHI: Dr. Adamson.

5 DR. ADAMSON: I think the response that  
6 Dr. Guttenplan made I would echo, that we have to  
7 remember this is a TD50 or benchmark dose based on  
8 rodent data and that the human data both with regards  
9 to activation of the carcinogen and the alkylation may  
10 be different. So, we have to keep that in mind. But  
11 at the present time, I would agree the best we can do  
12 is either use the TD50 or benchmark dose in rats. But  
13 I think further work needs to be done to try to relate  
14 this to humans.

15 DR. ATRAKCHI: Dr. Cronin.

16 DR. CRONIN: Yeah, thank you. I firmly  
17 agree with all of the previous comments, and when  
18 considering classification, we need something to base  
19 the classification on. We have the TD50. We also  
20 have the possibility of going to BNDL. I think, as  
21 well, from my perspective, it would be interesting to  
22 review the data and see if we are just going to

1 classify as carcinogenic-noncarcinogenic, that is one  
2 issue. If we want to look for potency classifications  
3 within the data, then we need to look at the data, and  
4 I am aware, for instance, from Professor Eisenbrand's  
5 presentation, we talk about high potency. We talk  
6 about low potency. And there have been some efforts  
7 to quantify that a little bit more. So, can we  
8 investigate the data to see if there are natural  
9 fallouts in terms of TD50 or the BNDLs in terms of  
10 potency. I also take on board all of the comments  
11 about reactivity and metabolism. I am intrigued to  
12 know is there a direct correlation between reactivity  
13 and carcinogenic potency. I suspect not because of  
14 all of the other issues that are involved in it. That  
15 is something again we need to tease out. Can we  
16 measure reactivity itself? We have done in other  
17 instances. For instance, for protein binding, or  
18 probably we have less data for reactivity for DNA  
19 binding. And I am intrigued by the suggestion. I had  
20 not really thought it before, but I think it is an  
21 excellent suggest to consider biomarkers, measures of  
22 reactivity, particularly if we can extrapolate up or

1 we can use human data.

2 I would also like just to  
3 think -- obviously we need short-term and FDA needs  
4 short-term achievable goals. A lot of those have been  
5 articulated but also to think where we are going in  
6 the future with aspects such as classification. I  
7 would just like to raise the issues. For instance, it  
8 can be given by Bayesian modeling probabilistic-type  
9 modeling of how we can incorporate data, how we can  
10 incorporate knowledge in different lines of evidence.  
11 So, that could be structural activity relationships.  
12 That could be biomarker data or metabolism-type data.  
13 And the reason I raise this is because it does give us  
14 the possibility of being able to assign some kind of  
15 level of probability and certainty to prediction. And  
16 I am very taken by the thoughts in the moment of  
17 rather than thinking of a TD50 as a single value, it  
18 is a distribution, and what we are trying to do is  
19 narrow that down to make a decision. Such as, for  
20 instance, to be able to find acceptable intake values.

21 With regard to acceptable intake  
22 values, I do not have any more specific comments. It

1 does seem a little bit analogous to TTC. I know that  
2 is probably a strange thing to say as we have already  
3 identified the nitrosamines as the cohort of concern,  
4 which is automatically removed from TTC, but maybe  
5 there are other ways or more data or more knowledge we  
6 can take from the TTC paradigm. And just to mention,  
7 there will be a workshop in Europe in the next few  
8 weeks on carcinogenicity and updating the TTC paradigm  
9 for that. Other than that, I do not have any more  
10 comments. Thank you.

11 DR. ATRAKCHI: Thank you. And  
12 Dr. Kyrtopoulos.

13 DR. KYRTOPOULOS: Thank you. I think  
14 it has all been said actually. The only thing I would  
15 add is that because a number of people refer to this  
16 issue of using biomarkers, in other words the DNA  
17 adducts generated by the nitrosamines. The extent to  
18 which they could serve as markers for potency or  
19 markers of risk and so on. The trouble is that  
20 despite all of the work that is being done on the  
21 nitrosamines, I do not think that we really understand  
22 the mechanism by which all the carcinogenesis in

1 sufficient detail. For the simple ones like  
2 dimethylnitrosamine, the other methylating nitroso  
3 compounds, methylnitrosourea, and so on. Okay,  
4 O6-methylguanine seems to be potent in various animal  
5 models. But the minute you go to more complex  
6 structures, and especially with regard to the  
7 chemicals out of concern in relation to the current  
8 issue, drug contamination, where the structures are  
9 quite varied, and I do not think that some of them are  
10 quantitated, and certainly the cyclic nitrosamines and  
11 so on, we do not really know whether it is  
12 O6-alkylation or whatever other adducts are. So, I am  
13 not really very optimistic that they would be, based  
14 on what we know today, a very practical guide toward  
15 helping us to classify. I guess if a chemical is  
16 giving rise to O6-methylguanine, yes, it would be  
17 likely to be a more potent carcinogen, but that does  
18 not tell us much about many of the other chemicals.  
19 So, I would eventually fall back to animal  
20 carcinogenicity combined with some expert judgment in  
21 relation to chemical metabolism, conversion to  
22 alkylating agents, and so on along the lines, which

1 have been presented previously. That is it.

2 DR. ATRAKCHI: Thank you very much. We  
3 are close to a break of 10 minutes, but before we go,  
4 I would like to ask all the other panelists if anyone  
5 has anything to add for the first two questions that  
6 we went through right now. Please go ahead if you  
7 would like to comment.

8 DR. HECHT: Yes. This is Steve Hecht.  
9 I think we need better measurements. I think there  
10 are way now to look at DNA adduct formation in humans,  
11 and I think we need to do that more thoroughly, more  
12 precisely, more reliably using the currently available  
13 high-resolution mass spectrometric methods to really  
14 determine how much relevant DNA damage comes from  
15 nitrosamine formation and nitrosamine exposure in  
16 humans. So, I do not think we really have that data,  
17 and it is quite critical for the risk assessment.  
18 Thank you.

19 DR. ATRAKCHI: Thank you. Anyone else?

20 UNIDENTIFIED PANELIST: Dr.  
21 Kyrtopoulos, you gave some data from the blood levels  
22 of 06-methylguanine and sort of extrapolated back to



1 an intake of dimethylnitrosamine. Is there any way to  
2 determine how much of that came from DNN and how much  
3 came from other sources?

4 DR. KYRTOPOULOS: Well, not directly,  
5 but as I indicated in the beginning, I am aware of  
6 maybe a dozen chemicals, to which potentially there is  
7 human exposure and which are capable of methylating  
8 DNA. There is s dimethylnitrosamine. We know other  
9 chemicals to which humans are not likely to be exposed  
10 like methylnitrosourea. There are also chemicals like  
11 dimethylsulfate, iodide, and so on. There are  
12 medicine drugs such as temozolomide, which all give  
13 rise to DNA methylation. We worked with quite a few  
14 of those chemicals in experimental animals, in  
15 rodents, and it turns out that NDMA really stands out.  
16 It is the most efficient generator of 06-methylguanine  
17 in blood DNA. I emphasize that I am speaking about  
18 blood because blood does not metabolize nitrosamines.  
19 So, it gets methylated as it goes through various  
20 tissues that generate the intermediate methylating  
21 agent. So, keeping in mind how likely people may be  
22 exposed to these chemicals that I have named, one does

1 not have very much left. Endogenously generated amino  
2 acids, glycine for instance. Carboxymethylate and  
3 methylate, so that is a potential source of endogenous  
4 methylation. However, from the data that we have, the  
5 methylating ability of that intermediate because it is  
6 a stable chemical seems to be quite low. So, taking  
7 everything into account, animal data, animal  
8 dosimetric data and human exposures, NDMA seems to be  
9 the most likely source of this adduct.

10 UNIDENTIFIED PANELIST: How about NNK?

11 DR. KYRTOPOULOS: NNK on a per dose  
12 administered dose basis it methylates much less than  
13 NDMA. Dr. Hecht may have the numbers. I do not have  
14 them in my mind right now, but I remember at the time  
15 when we worked on it, it could not be compared with  
16 NDMA.

17 DR. HECHT: Yes, that's correct. We  
18 compared that -- we published a paper in 1986 on that.  
19 NDMA is a better methylating agent, but also NMK.

20 DR. KYRTOPOULOS: That's right.

21 DR. ATRAKCHI: Okay, then. Thank you  
22 very much. And we will take now a 10-minute break,

1 and we'll resume at 11:40. Thank you.

2 MS. PAINTER: All right. It is just  
3 one minute after 11:40, so, we are going to begin with  
4 the next question.

5 Just as a reminder for everybody,  
6 please utilize the Q&A box, to submit your questions.  
7 While we do have a team of people moderating the  
8 questions, please know that we will not send a  
9 response. However, if you see that your question is  
10 dismissed, that means that it has been received and  
11 sent to the moderators. Thank you.

12 DR. ATRAKCHI: Thank you. We move on  
13 now the third question.

14 The carcinogenic potential of  
15 nitrosamines is dose and duration dependent. Is there  
16 an in-vivo exposure level for nitrosamines that could  
17 define low versus high risk for carcinogenicity? Is it  
18 appropriate to calculate a now-observed-effective-  
19 level dose for carcinogenicity? What are the criteria  
20 to do so? Would a resultant in an Ames negative be  
21 adequate, in vivo mutation assay negative, or another  
22 other test?

1           The second part of the question is can  
2 a less than lifetime approach as described in M7  
3 Guidance be used to determine the acceptable intake of  
4 nitrosamine if the drug is indicated for a short  
5 period of use?

6           Based on the discussion so far with the  
7 understanding that humans are exposed endogenously and  
8 exogenously to nitrosamines, we know some of the  
9 pharmacokinetics. We also know that DNA repair  
10 capacity varies tremendously among humans as well as  
11 among animals. And there is also the less ideal  
12 quality of the carcinogenicity studies conducted with  
13 nitrosamines. With all of this in mind, can a NOEL be  
14 identified with confidence? Some of the studies have  
15 shown clear and abrupt transition to a no effect.  
16 Other chemicals showed gradual change with a  
17 curvilinear dose response and a sigmoidal in the low  
18 dose. Another consideration to keep in mind is the  
19 dose rate, is the interval between the doses and how  
20 would this affect the DNA repair. Earlier studies  
21 have show cancer rate is independent on age, and DEA  
22 for example when administered at the same dose to

1 animal species of different life expectancies all  
2 animals developed tumors at the same rate and time.  
3 Regarding the second part of the question, a  
4 less-than-lifetime approach, how reliable are the  
5 models that extrapolate from long to short duration.  
6 What is the model sensitivity and the shape of the  
7 response, nonlinear versus threshold, for example. In  
8 the end, can an acceptable cancer risk be achieved  
9 based on exposure to a predefined limit for one or  
10 more nitrosamines that are known to be potent  
11 mutagenic carcinogens when exposed only for a short  
12 period of time?

13 We will start with Dr. Bucher.

14 DR. BUCHER: Thank you. You laid out a  
15 large number of questions there that are quite  
16 difficult to respond to, but I will start with the  
17 question of whether there is an in-vivo exposure level  
18 for nitrosamines that could define low versus high  
19 risk for carcinogenicity. I think that one must  
20 simply take a practical approach to this question and  
21 look at the approach that has been laid out in the  
22 European Medicine Agency's report. As an example, a

1 practical answer would have to be that an in-vivo  
2 exposure level of high-risk would simply be the  
3 adjusted human dose representing more than a 1:100,000  
4 risk calculated based on the carcinogenic potency  
5 database. This would mean that a nitrosamine dose of  
6 high risk would be one with a TD50 extrapolated dose  
7 of greater than 1.5 mg/kg per day for a nitrosamine  
8 with a TD50 less than 1.5 mg/kg per day. By  
9 definition then, a human nitrosamine exposure of low  
10 risk would be an extrapolated TD50 dose of less than  
11 1.5 mg/kg per day for a nitrosamine with a TD50  
12 greater than 1.5 mg/kg per day.

13           And with respect to the second question  
14 about it, is it appropriate to calculate a NOEL dose  
15 for carcinogenicity? I personally do not think that  
16 the concept of an experimentally derived NOEL is  
17 appropriate for genotoxic carcinogens and generally  
18 for genotoxic compounds in general. In the example I  
19 just mentioned, the NOEL is in essence the dose  
20 defining the risk level low or below 1:100,000 because  
21 this is a generally agreed upon acceptable level. A  
22 second hypothetical NOEL in the dose where the

1 additional risk from exposure to an exogenous  
2 nitrosamine falls below the risk from nitrosamines  
3 that are generated endogenously. In this case, I see  
4 two ways of looking at this information. One is that  
5 a low NOEL would simply be the exposure dose where the  
6 risk presented by the exogenous nitrosamine is below  
7 the absolute total risk from endogenously generated  
8 nitrosamines. The counterview would ignore the risk  
9 from endogenously generated nitrosamines and consider  
10 that exogenous nitrosamine exposures would always  
11 present an additional incremental risk that can be  
12 calculated as in the example I mentioned earlier. I  
13 believe the second view is more ethically defensible  
14 and that an incremental risk is still a risk. I note  
15 that this concept is going to be further discussed and  
16 addressed in Question 5, so I will leave it at that  
17 for now.

18           With respect to the less-than-lifetime  
19 acceptable daily intake approach as outlined in the  
20 ICH M7 Guidance, I understand the concerns, especially  
21 those that you mentioned, given the experimental  
22 animal cancer data that might lead one to question

1 whether this is an appropriate practice based on data  
2 on the observations of the higher potency of some of  
3 these nitrosamines if given in say high dose post  
4 dosing rather than in long lifetime lower-level doses.  
5 But I am in general agreement that given low doses  
6 that correspond to the very low risk levels that we  
7 are talking about, the 1:100,000, that to exceed the  
8 acceptable lifetime intake levels for shorter periods  
9 of time probably does not represent an unreasonable  
10 risk for adults and likely for patients starting even  
11 at younger ages. But when you consider that some of  
12 these models of short-term rodent cancer studies,  
13 especially the neonatal mouse model, in particular in  
14 their response to short exposures to genotoxic agents  
15 showing carcinogenesis, I would suggest that based on  
16 these that the risks of the less-than-lifetime  
17 approach may be more significant in children, and I  
18 think that this whole area needs a whole lot more  
19 discussion and careful consideration. Thank you.

20 DR. ATRAKCHI: Thank you. Dr. Adamson.

21 DR. ADAMSON: I would agree that use of  
22 the dose for additional risk of 1:100,000 would be



1 appropriate. I would say to use the benchmark dose  
2 rather than the TD50 would be appropriate from the  
3 rodent data, remembering you are extrapolating from  
4 the rodent data. But I would also say that with  
5 regards to the second part of the question about a  
6 lifetime approach, yes, I think it is appropriate  
7 because I believe that the induction of cancers, dose  
8 times time plus the repair mechanism, so I think the  
9 use of a lifetime approach is fine, but if it is a  
10 short duration of use, I think the present application  
11 that FDA uses is appropriate to determine the dose.

12 DR. ATRAKCHI: But are you saying that  
13 the use -- you are agreeing to use the  
14 less-than-lifetime approach if the medicine is used  
15 for a shorter period, not a chronic use, you are  
16 agreeing to adjust for that or not?

17 DR. ADAMSON: Yes, I'm saying that I  
18 think you can adjust for the fact that it is less than  
19 a lifetime use.

20 DR. ATRAKCHI: Okay. Dr. Kyrtopoulos.

21 DR. KYRTOPOULOS: Yes. Well, I am  
22 trying to think a little bit in kinesthetic terms. I

1 would like us to remember the Peto rat mega bioassay  
2 that is used to derive what is today considered the  
3 acceptable intake. In that study, what they observed  
4 a dose response curve for the induction of liver  
5 cancers, which was hockey stick-shaped as it was  
6 called. We have the slide. On the right, the dashed  
7 lines show the dose response for the induction of  
8 different types of liver cancer in the Peto bioassay.  
9 It was expressed with it by a parameter called the  
10 Weibull index. And you can see that at a dose rate of  
11 about 200 mcg/kg per day, there is a sharp upward  
12 turn. However, below that exposure, the dose response  
13 curve was described by Peto as linear with no evidence  
14 of a threshold. And this linearity in absence of a  
15 threshold ties up with the data that we have on  
16 adducts in rat liver, which is a continuous line  
17 above. This is the data formation from an animal  
18 which basically replicated, repeated the Peto  
19 bioassay. And you can see that the other dose  
20 response is pretty linear all the way down to very low  
21 doses. So, there is no break in the other dose  
22 response curve. What happens around 200 mcg/kg per

1 day is that there is an increase in the induced cell  
2 proliferation in the liver, and that is one factor,  
3 which contributes to this upward turn of the  
4 carcinogenesis exposure response. So, both on the  
5 basis of the bio assay and the adducts dose response,  
6 the dose response at low dosages is linear, and there  
7 is no evidence of a threshold. We should say, of  
8 course, that this is what happens in animals, in the  
9 rats. We do not know whether the same thing applies  
10 to humans, and it is actually something that was  
11 already pointed out in the Peto paper. However, based  
12 on what we know from the animal data, we do not see  
13 any evidence of a no-effect dose.

14 So, can turn to the second question  
15 regarding the application of a less-than-lifetime  
16 approach? Carcinogenesis is a function of the  
17 accumulated dose, the accumulated carcinogenic damage.  
18 But it also depends on additional factors as we see.  
19 It may be cell proliferation, maybe other biological  
20 phenomenon, apoptosis, and so on. As far as the DNA  
21 damage part is concerned, the fact that we have linear  
22 dose response means that it is defensible. It is

1 acceptable to accept an exposure to a higher dose for  
2 a shorter period of time because the integrated  
3 overall lifetime exposure in terms of DNA damage would  
4 remain the same. On the other hand, we do not know  
5 what the dose response relationship is with regard to  
6 the other factors, which contribute to the  
7 carcinogenesis overall. So, we do not know how cell  
8 proliferation or the reduction of cofactors and so on  
9 may vary if temporarily increase the dose. It is not  
10 so easy to say that the effect of a higher dose for a  
11 shorter time is equivalent to a lower dose for a  
12 longer time. Nevertheless, on the other hand, we do  
13 have the real problem of the possibility that we may  
14 have to live with the presence of an undesirable  
15 chemical in a medicinal product. So, I think the  
16 overall evidence that we have here would make it  
17 possible -- it would be acceptable for me to accept a  
18 higher than the lifetime-acceptable intake limit.  
19 However, one should have in mind the unknowns, which  
20 are present, and keep this exceedance as low as  
21 possible. That's all.

22 DR. ATRAKCHI: Dr. Zeiger.

1 DR. ZEIGER: Thank you. My comments  
2 are mostly regarding to calculation of a NOEL dose of  
3 carcinogenicity. And I've never been a big fan of the  
4 NOEL calculation because it is very highly dependent  
5 on the test protocols that are used to generate the  
6 data. For example, you know, most carcinogenicity,  
7 most in-vivo mutagenicity studies are done at subtoxic  
8 doses for in-vivo for long-term subtoxic doses,  
9 whereas the human exposure is generally on orders of  
10 magnitude lower. And we assume that there is a linear  
11 extrapolation, but also that extrapolation is based on  
12 the dosing and dosing regimen that is used in the  
13 studies. I think we already classify chemicals of  
14 nitrosamines as Ames test negative and Ames test  
15 positive. With Ames test positive being presumed to  
16 be carcinogenic unless they are shown otherwise. And  
17 the majority of Ames test negative studies to my  
18 knowledge are noncarcinogenic. With regard to using  
19 in-vivo mutation assays, we do not have that much data  
20 on nitrosamines from the in-vivo studies. The in-vivo  
21 studies tend to be less sensitive than the in-vitro  
22 studies, and they are also conducted at high subtoxic

1 or up to toxic doses, but the advantage to them is  
2 they are done on blood cells, whether red or white  
3 blood cells, which have been shown earlier to be good  
4 indicators of the maximum DNA damage dosing you are  
5 going to get in-vivo. So, the mutagenicity of gene  
6 tox studies can be used to at classify the  
7 nitrosamines, but with regard to the potency, I am  
8 still stuck with the information that I have that the  
9 potency at least in the in-vitro studies does not  
10 predict the potency in-vivo, and we do not really have  
11 much data to determine how well the potency of the  
12 in-vivo mutation assays will predict the predict the  
13 potency of the cancer assays. The DNA adduct data may  
14 be linear, but to go from the DNA adduct to a mutation  
15 requires a number of steps, some of which are toxic,  
16 some of which will produce a mutation. Then, to go  
17 from the mutation to the cancer, you need another  
18 number of stages, any one of which could fail and not  
19 give you a cancer result. So, the linear  
20 extrapolation from an adduct to a mutation is still  
21 very tenuous. I think we have seen that the adduct to  
22 mutation studies where we have the data tend to be

1 nonlinear in appearance.

2                   With regard to the less-than-lifetime  
3 approach, I think that is an important consideration.  
4 And as we have shown in some of the neonatal mouse  
5 studies, which are mentioned, a short-term dosage  
6 approach in younger animals, in neonates, can give you  
7 different results than the same approach in adult  
8 animals. So, the less-than-lifetime approach really  
9 needs to be investigated a lot more with regard to  
10 nitrosamines.

11                   And I think that's it for me.

12                   DR. ATRAKCHI: Thank you. Dr.  
13 Eisenbrand.

14                   DR. EISENBRAND: Everything has been  
15 said already to that question. I think personally I  
16 would not favor very much an NOEL approach. In my  
17 opinion, it is better to use the BNDL approach,  
18 especially since the BNDL approach takes consideration  
19 of the whole dose range with a specific regard to the  
20 low-dose range. And that is why I think it appears to  
21 me as more stringent than the TD50 based values  
22 concerning NOEL. And that is the one thing. The

1 other thing, the correspondence between Ames positive  
2 or negative and carcinogenicity positive and negative,  
3 which Zeiger had already alluded to very convincingly.  
4 So, to me the less LTL approach, the second question,  
5 I think the reservations concerning the LTL approach  
6 consider mainly because of the possibility of  
7 intervening repair. And I think this question needs  
8 to be decided with respect to the expectable dose that  
9 is being taken up by the drug as a contamination or by  
10 other ways because this fear that the repair,  
11 especially the demethylase repair, the  
12 O6-demethylating repair may be not really substantial  
13 in this very low dose that we are discussing at the  
14 moment. So, from this point of view, I would think,  
15 yes, one could use the LTL approach at least for a  
16 certain time until scientific evidence shows that it  
17 is useful or even it is not. In that relation, I  
18 would also mention that there has been a very thorough  
19 dose response study by the Dulthai [ph] Group many  
20 years ago in the '60s where they used DNA in very  
21 widely spaced daily dosage, coming from the upper end  
22 of about 10 mg/kg down to as low as 70 mcg/kg



1 bodyweight. And there it is quite interesting to see  
2 that the slope of all these dose responses remains  
3 very parallel, very similar down to the lowest level,  
4 which still within a lifetime I most say, an extended  
5 lifetime of three years of the rats still produced  
6 tumors. So, the overall cumulative dose diminished in  
7 response to the lower daily dose quite significantly,  
8 which shows that even at the very low dose end and of  
9 70 mcg/kg bodyweight per day, there is a sort of --  
10 without any losses actually of the carcinogenic  
11 activity. Let's say the DNA mutations used by  
12 diethylnitrosamine, there is still a clear dose  
13 response seen. So, they calculated from this dose  
14 response, the time dose with an exponent of 2.3, so it  
15 is a very important parameter to consider that the  
16 time of these nitroso compounds goes in a  
17 relationship. And so, maybe that the LTL approach  
18 really is defensible when we are in the very low dose  
19 range. The dose range should be connected to  
20 induction of tumors, at least as animal experiments  
21 teach us.

22 DR. ATRAKCHI: So, to your point

1 towards the end, do we know with reasonable accuracy  
2 that the DNA repair mechanisms in enzymes do not get  
3 saturated, animals or humans, when we give a large  
4 dose of a nitrosamine? And that is not  
5 necessarily -- we have to clearly understand whether  
6 this nitrosamine is coming from the medicine, not only  
7 the medicine alone, but obviously we need to take into  
8 consideration the collected totality of all sources of  
9 nitrosamines that are taken in. We do say it is dose  
10 and duration dependent, so going to taking a big dose  
11 of nitrosamine, are we saying that is okay to adjust  
12 because the DNA repair mechanism is capable of that.  
13 And so, I have another question, but can anyone  
14 comment on this?

15                   Perhaps to address your question  
16 directly, the question always is what is a big dose.  
17 I would not think that in the dose response  
18 relationship the upper dose range would be useful to  
19 consider. I think that this exercise in risk  
20 assessment beyond the lower dosage definitely. If not  
21 on a very low dosage, and there I think it is probably  
22 not really of great relevance that we have to consider

1 saturation effects of this demethylase. As soon as  
2 you go into the higher dosage, then certainly you have  
3 this quite clear.

4 DR. ATRAKCHI: Okay.

5 DR. ZEIGER: I'd like to address this.

6 DR. ATRAKCHI: Yes, please.

7 DR. ZEIGER: Remember, there are some  
8 studies many, many years ago with regard to you  
9 talking about DNA repair enzymes but also metabolic  
10 enzyme, whether they are saturable. I recall some old  
11 VMN studies where once you get above a certain dose of  
12 VMN -- I don't remember if it was rat or mouse -- that  
13 you start getting kidney tumors in addition to the  
14 liver tumors because you are saturating the liver  
15 metabolic capability. With regard to DNA repair  
16 enzymes, there are two different categories. There  
17 are those that are constitutive, which means you  
18 always have a certain level of that repair enzyme  
19 available in the cell to address the damage, but you  
20 also have the inducible enzymes, which means you have  
21 to get to a certain level of DNA damage before that  
22 enzyme is induced. So, you can get saturation in a

1 way. You can get saturation of the constituent  
2 enzyme, and presumably, you should also be able to get  
3 saturation of the inducible enzyme at high enough  
4 levels of damage.

5 DR. EISENBRAND: I totally agree with  
6 that. I mean, that's quite clear that you can get  
7 separation, especially the experiments where we  
8 receive the kidney tumors that happens at high  
9 dosages, sometimes even at one single dose. You do  
10 not see liver, but you see kidney tumors. But as I  
11 said, I think we need to mainly concentrate on the  
12 low-dose range because I would not think or I would  
13 not expect that enzyme saturation plays any role with  
14 the dosage where we are here.

15 DR. ATRAKCHI: And this is even taking  
16 into consideration the exposure from the number of  
17 sources that we have already discussed from the  
18 environment, from the food. The people's habits.  
19 Some of them will eat a lot of smoked foods, smoked  
20 fish, and so on. We are not only addressing the level  
21 of nitrosamines in the drugs. We know these are  
22 comparable to other sources that could be lower. You

1 all are taking that into consideration, the multiple  
2 sources, is that correct?

3 DR. EISENBRAND: Well, by and large, my  
4 impression is that from the multiple sources we have  
5 to consider, it is mainly the food because water is so  
6 low that in that sense I do not think of any  
7 relevance. And the exposure from food still is very,  
8 very low. I mean it is in the low microgram a day  
9 range, which is nanogram/kilogram body weight. So, I  
10 would not expect that it is the nitroso compounds  
11 themselves, if there is any influence on enzymes that  
12 activate or deactivate in terms of saturation, as well  
13 as in terms of repair adducts.

14 DR. ATRAKCHI: Okay. One more  
15 question. It seems like at least based so far on the  
16 discussion that potentially the less-than-lifetime  
17 approach could be applicable to the nitrosamines that  
18 we are addressing here. If that is the case, would  
19 safety factors need to be considered and incorporated  
20 based on age? And I say this because -- first of all,  
21 M7 does not ask and does not require additional safety  
22 factors. That is one issue is that it is not -- we do

1 not use safety factors in M7. Also, our colleagues in  
2 the Center for Foods in FDA do not adjust for longer  
3 lifespans, and they use models that they estimate how  
4 much specific food ingredients is consumed based on  
5 surveys of dietary habits. For example, they can  
6 limit the analysis to people who consume cheese on a  
7 daily basis. Nevertheless, EPA does not assess for  
8 carcinogenic impurities in fruits, but they do use  
9 safety factors to determine limits in pesticides that  
10 are used on foods. So, would you recommend adjusting  
11 for less-than-lifetime between let us say pediatric  
12 indications versus adults -- medicines used for  
13 adults? This would be somewhat not under the guidance  
14 of M7, but would you recommend that based on the  
15 nitrosamine as carcinogens.

16 DR. BUCHER: This is John Bucher. This  
17 is a very difficult question, of course, and I think  
18 that one might pay attention to any kind of  
19 information that is available concerning the  
20 development of aspects of various repair enzymes  
21 according to age. Pay attention to the P450 profile  
22 changes with respect to the developing individual.

1 Certainly, we know they change probably in life.  
2 Conjugation reactions change, so all of these things  
3 tend to contribute I think to a higher sensitivity of  
4 early life stages to carcinogenic exposures. So, I  
5 think that unless one takes into consideration the  
6 profile of all of these activities, it is really hard  
7 to decide whether you need to particularly adjust by a  
8 certain factor. That would be my response.

9 DR. ATRAKCHI: Thank you. And  
10 Dr. Kyrtopoulos, would you like to comment?

11 DR. KYRTOPOULOS: I'd like to say  
12 something about the previous discussion on this  
13 question of DNA repair and how it may be affected if  
14 one is exposed temporarily to higher doses. I really  
15 do not think that with the kinds of exposures that we  
16 are speaking about even though once potentially coming  
17 from the contaminated drugs, there is any likelihood  
18 of any significant exhaustion or any significant  
19 depletion of the alpha transferase. If you just look  
20 at the diagrams from the Peto study where the exposure  
21 rates that were used, they go up to quite large doses.  
22 In the animal experiment that we did, there was no

1 depletion, no change in the alpha transferase in the  
2 MGMT levels throughout this range. And if you think  
3 about the adduct levels that are likely to be  
4 generated following an intake of a contaminated drug  
5 containing NDMA, I think that the adduct levels that  
6 are likely generated, it is concerning. But I think  
7 it is very unlikely that they would significantly  
8 impact on the pull of the repair enzyme. So, I would  
9 not count this factor as one of the items to consider  
10 in trying to decide whether an LTL approach is  
11 applicable or not.

12 DR. ATRAKCHI: Thank you. I'd like to  
13 ask Dr. Rice to make comments on this question, on  
14 Question 3.

15 DR. RICE: (No response.)

16 DR. ATRAKCHI: Would anyone else like  
17 to comment? We'll get back to Dr. Rice in a moment.

18 DR. ZEIGER: Yeah. I have a comment.  
19 We have been considering thresholds mainly with  
20 response to data on liver carcinogenesis, and that it  
21 is very unlikely it gets saturated at doses that would  
22 be achieved just by intake of contaminated drugs. How



1 about other organs, though? What is known about the  
2 capacity, the O6-methyltransferase repair in other  
3 organs? Does anybody know?

4 DR. KYRTOPOULOS: May I come in? May I  
5 respond?

6 DR. ATRAKCHI: Of course. Certainly.

7 DR. KYRTOPOULOS: The alpha transferase  
8 has been measured in a number of human tissues. As  
9 far as primary human tissues are concerned, they all  
10 contain quite significant levels. The liver usually  
11 has the highest level, but the lowest levels that have  
12 been measured maybe let us say five times less. Even  
13 in tissues with relatively low levels of alpha  
14 transferase, this is orders of magnitude higher than  
15 the level of others that we are likely to see coming  
16 from all of the environmental exposures and the  
17 contaminated drugs. Of course, there is always the  
18 possibility that there may be small subpopulations of  
19 cells, which are even more repair deficient. But  
20 again I emphasize as far as primary human cells are  
21 concerned, I am not aware of any deficiency. Cancer  
22 cells? Yes. There are cancer cells where the

1 expression of the MGMT has been lost but not in  
2 primary -- I am not aware of data in primary cells  
3 showing such an effect.

4 DR. ADAMSON: Thank you. I would like  
5 to make a comment on this question.

6 DR. ATRAKCHI: Of course.

7 DR. ADAMSON: We did an experiment in  
8 nonhuman primates primarily Cynomolgus monkeys to do a  
9 dose response to administration of diethylnitrosamine,  
10 and we used at least 10 animals per dose starting at  
11 six months of age. And what we found with the  
12 diethylnitrosamine giving doses of 40, 20, 10, 5, 1,  
13 and 0.1 mg/kg once per week. A clear dose response  
14 occurred. At the lower doses, we did not get any  
15 tumors at all as long as we did the experiment and  
16 when the monkeys were sacrificed, nor did we determine  
17 any lesions in the liver or in the organs. That was  
18 about 16 years after dosing. The lifetime of  
19 cynomolgus monkey is about 20 years. At the lowest  
20 dose, only 10 animals per group. At the highest dose,  
21 we got 100 percent tumors of the dose of all of the  
22 animals, and there was dose response with regards to

1 both the latent period, as well as percentage of the  
2 tumors. And it was a pretty linear response until we  
3 got to 5 mg/kg and at 1 mg/kg. We got 40 percent of  
4 the animals. Again at 0.1 mg/kg, there were no tumors  
5 when the study was stopped. Minimally, this is only  
6 10 animals per group, but it is administration of a  
7 very potent carcinogen, diethylnitrosamine, which at  
8 that top dose 40 mg/kg, we got 100 percent of the  
9 animals with a hepatocellular carcinoma. So, there is  
10 a clear dose response and a clear latent period over  
11 the lifetime of the animals.

12 DR. ATRAKCHI: Thank you. Dr. Rice,  
13 would like to commend on Question 3?

14 DR. RICE: Thank you. I am having  
15 considerable difficulty with the signal fading in and  
16 out here. I do not have specifics to add to this, but  
17 I want to express some concurrence with first the  
18 caution expressed about calculating the NOEL dose of  
19 carcinogenicity with a potent genotoxic agent like any  
20 of the nitrosamines under discussion. And I do not  
21 think it is really practical in a comparatively  
22 low-dose range to attempt to identify in-vivo exposure

1 that would rather absolutely define low versus high  
2 risk. I do not see how the continuum, that is  
3 response, can readily be found in these agents,  
4 except, of course, as the dosage becomes very, very  
5 much higher in any of those that would be experienced  
6 by anyone from taking any of the drugs that are under  
7 consideration. With that, I have nothing more to add.

8 DR. ATRAKCHI: Thank you. I would like  
9 to go back to one point we made here in the question,  
10 which is Ames negative. We use Ames negative as the  
11 first step or the first test to determine if a  
12 chemical is mutagenic or not. Some of those  
13 nitrosamines could test negative in the Ames test.  
14 This is difficult for us to decide that this would be  
15 acceptable, even though the Ames test was conducted  
16 properly under GLP in a valid test, but the result is  
17 negative. What would you recommend? Would you accept  
18 a single, well-conducted valid Ames test to conclude  
19 that a particular nitrosamine is negative, is not a  
20 mutagenic agent? Or would you follow this up with an  
21 in-vivo gene mutation test or any other followup  
22 mutation test to verify the negative result?

1 DR. ZEIGER: This is Dr. Zeiger. With  
2 regard to the negative Ames test for nitrosamines, the  
3 response on the Ames test for the nitrosamines is very  
4 species specific and very protocol specific.  
5 Initially, dimethylnitrosamine was reported as  
6 negative in the Ames test until people started  
7 increasing the relative liver homogenate concentration  
8 to VMN concentration, and then it became positive.  
9 Similarly, you have different potencies of responses  
10 when you test the same chemical using rat liver, mouse  
11 liver, or hamster liver, to the extent if you are  
12 using rat liver, which tends to be the least sensitive  
13 to the nitrosamines, you might get a very weak or  
14 negative response with rat liver but might get a  
15 fairly potent response if you are using mouse liver or  
16 hamster liver. We do not know which one of those  
17 livers is most comparable to what would be obtained  
18 with humans. So, as far as I am concerned, even a  
19 negative mutagenicity study with nitrosamines, if the  
20 structure is such that you think it might be  
21 metabolizable. And Dr. Eisenbrand showed a number of  
22 structures early on that you would not expect to be

1 activated to alkylating agents. You know, if the  
2 structure does not tell you that it should be or might  
3 be negative, I would consider a negative Ames test as  
4 not sufficient to say it is not going to be a  
5 carcinogen.

6 DR. ATRAKCHI: Thank you. Anyone else  
7 would like to comment?

8 DR. ADAMSON: I would think you would  
9 want to follow up with an in-vivo mutation assay  
10 before I would accept a negative Ames test as being  
11 possible.

12 DR. ZEIGER: I agree to some extent,  
13 but the in-vivo assays tend to be less sensitive,  
14 though it does not hurt to look at the in-vivo assays.  
15 They are getting better every day. We are now able to  
16 look fairly easily at gene mutation, as well as  
17 chromosomal mutations in red blood cells, mutations  
18 that were induced when the cell was still nucleated.  
19 So, a positive in-vivo assay would trump negative  
20 in-vitro assay. I agree with you on that. But  
21 because of the variations and responses with different  
22 protocols in the in-vitro assay, I would be reluctant

1 to conclude that something is negative based on a  
2 single assay with, for example, rat liver S9. Using  
3 the standard OECD protocol. The OECD protocol is a  
4 minimum protocol. It is not the definitive protocol.

5 DR. ATRAKCHI: Thank you. Anyone else  
6 who would like to comment on this?

7 DR. ADAMSON: Yes. The in-vivo  
8 mutagenesis assay picks up a number of compounds. I  
9 do not know about nitrosamines but some related to  
10 nitrosamines like dimethylhydrazine, which are  
11 negative in the Ames assay but are positive in in-vivo  
12 mutagenesis assays. So, it is a good followup, but of  
13 course, it is a lot more expensive and a lot more time  
14 consuming.

15 DR. ATRAKCHI: Thank you. So, I  
16 understand that even though not everybody responded to  
17 this question, but the general agreement is that a  
18 negative Ames by itself is inadequate to conclude that  
19 the compound is negative for mutagenicity.

20 There is one question from the  
21 attendees. I will read it. Would experts consider  
22 there is a limit maximum exposure for less than

1 lifetime and number of nitrosamines in a drug product?  
2 Multiple nitrosamines in drug products are not limited  
3 in M7. The less-than-lifetime allows 80-fold  
4 acceptable intake for 30-day treatment, so that  
5 theoretically, the total exposure for nitrosamines may  
6 increase to even milligram amounts. Would anyone like  
7 to comment on this?

8 I think that basically the question is  
9 what is a low-dose range for a nitrosamine exposure?  
10 Maybe that is what the question is.

11 UNIDENTIFIED PANELIST: Could I comment  
12 on that?

13 DR. ATRAKCHI: Absolutely, please.

14 UNIDENTIFIED PANELIST: Just as a  
15 pragmatic answer -- I mean I would personally orient  
16 myself on the unavoidable exposure from foods. The  
17 nutritional exposure is there, and I think it is in  
18 most cases, it is considered to be somewhat higher  
19 than the potential exposure from contaminated drugs.  
20 But of course, that has to be checked in any case. And if  
21 it comes to the mentioned dose level of milligrams, I  
22 would think this is in my opinion not feasible. It is



1 far exceeding the levels of nutritional exposure.

2 DR. ATRAKCHI: Thank you. Anyone else?

3 DR. KYRTOPOULOS: May I comment?

4 DR. ATRAKCHI: Yes.

5 DR. KYRTOPOULOS: Surely, it would  
6 depend very much on which nitrosamines we are speaking  
7 about. I mean the idea of affecting a milligram of  
8 NDMA even for a few days is just not something that  
9 one would consider. On the other hand, if it was  
10 something like a nitrosoproline, which I know is not  
11 the case for drugs -- I mean a noncarcinogenic  
12 nitrosamine, it would be a completely different thing.  
13 So, one has to look at specific cases. I do not think  
14 we can put -- it would be a case-by-case evaluation.  
15 I do not think we can put a general number on this.

16 DR. ATRAKCHI: Okay. Thank you very  
17 much.

18 So, we should probably now break for  
19 lunch. We will come back at one o'clock. Thank you  
20 very much.

21 DR. ATRAKCHI: Welcome back. It is  
22 1:01. Before we continue to the last question of

1 today, Question 4, I would like to go back to Question  
2 3 for a moment. It is fairly important for us as  
3 regulators to really understand a little bit better.  
4 With your responses and your thoughts and the reasons  
5 for your recommendations about Ames negative. The  
6 issue we face is that a nitrosamine will be tested,  
7 comes negative in Ames. They would repeat it. It  
8 would be repeated let us say with a blood product with  
9 a mouse or a hamster S9. The test becomes negative as  
10 well. So, let us address this scenario. Would that  
11 be convincing that this nitrosamine is negative in  
12 Ames? Is not a mutagenic nitrosamine and will end it  
13 there. And this means from a regulatory perspective  
14 that the next step is this impurity, nitrosamine  
15 impurity will be considered a regular impurity,  
16 meaning it will fall under ICH Q3A or B where it is  
17 controlled under much higher levels than an impurity  
18 that is mutagenic. So, it is a very important  
19 regulatory decision to make to allow such a one-test  
20 or two-test of a nitrosamine of a negative nitrosamine  
21 in an Ames test and then move it from the category of  
22 a cohort of concern to a regular impurity. We really

1 would like to understand from you your expertise and  
2 your knowledge of is this an acceptable or if one  
3 conducts an Ames with an S9 from the rat and it is  
4 negative, they follow it up with an Ames using a  
5 hamster S9, and it is negative, would they need to  
6 confirm because we may have missed something -- those  
7 tests have missed something -- and it has the nitroso  
8 group. It is on structural alert. Would this need  
9 to be confirmed in a followup test, whatever that test  
10 is? Whether it is an in-vivo mutation test or any  
11 other that from your experience would provide a more  
12 reliable result? Anyone who would like to comment?

13 DR. ADAMSON: I will start by saying I  
14 think that you need an in-vivo followup, not another  
15 in-vitro followup, regardless whether it is human  
16 liver, whether it is nonhuman primate liver, whether  
17 it is hamster. I think you need an Ames negative, and  
18 then you need an in-vivo assay negative, from my  
19 perspective.

20 DR. ATRAKCHI: Thank you. Anyone else?

21 DR. GUTTENPLAN: As I said before,  
22 there are certain compounds that are more sensitive --

1 DR. ATRAKCHI: Yes. Dr. Guttenplan?

2 DR. GUTTENPLAN: Yeah, as I mentioned  
3 before, there are certain chemicals that are more  
4 sensitive in the in-vivo metagenesis assay than in the  
5 Ames assay. And also in the in-vivo assays, you can  
6 give repeated doses over a longer period of time. So,  
7 the assay can be quite sensitive. As mentioned  
8 before, also, it is more time-consuming and more  
9 resource-consuming. And then assuming you exposed the  
10 animal for a sufficient time and sufficient dose and  
11 you get a positive result, what does that mean? That  
12 is another question. If you give enough of the  
13 compound for a long enough period of time, is that  
14 relevant to human exposure? So, that is just a  
15 question.

16 DR. ATRAKCHI: Now, when we are talking  
17 about in-vivo mutation assays from your  
18 perspectives -- there are a number of them. M7 has a  
19 number of them in their table over there in the  
20 Guidance. But clearly some of them are better than  
21 others and depending as you indicated on the compound  
22 itself, one would be preferable over the other. But,

1 which ones would you think for a nitrosamine would be  
2 more appropriate than other in-vivo mutation tests?

3 DR. GUTTENPLAN: I think for  
4 nitrosamines the Mutamouse assay, the Big Blue Assay.  
5 There is a Japanese assay. I think it is GDL Mouse.  
6 I am not sure of that, but that would also be another  
7 assay. Those are the ones that I am familiar with  
8 those, and those are pretty good for detecting  
9 particularly relatively small molecular weight  
10 lesions.

11 DR. ATRAKCHI: Very good. Thank you.  
12 Anyone else?

13 DR. HECHT: I think we have to consider  
14 the carcinogenicity database that we have for  
15 nitrosamines. There are very few nitrosamines that  
16 are noncarcinogenic, really only the nitrosamino acids  
17 with maybe a few other exceptions fall into that  
18 category. So, I absolutely agree with everything that  
19 has been said so far. Just a negative Ames is not  
20 enough. You need to do an in-vivo test. You need to  
21 have tested thoroughly before you can conclude that  
22 nitrosamine compound would be noncarcinogenic or

1 nonmutagenic. Thank you.

2 DR. ATRAKCHI: Yes. To your point, Dr.  
3 Hecht, and also to Dr. Guttenplan, your comment, what  
4 does it mean if it is in-vivo positive when the Ames  
5 was negative? You are correct, but from a regulatory  
6 perspective, the first test or group of tests, the  
7 battery of tests is mutagenicity. Ultimately, the  
8 concern is carcinogenicity for risk assessment. So,  
9 this is why it is essential, and it is important and  
10 critical for us to determine if the nitroso is  
11 mutagenic. It is the first step, and that is why we  
12 need to confirm if it is negative, why is it negative  
13 in a mutagenicity test. What we need to do is a  
14 followup, and that followup is an in-vivo mutation to  
15 further verify the organ metabolic mechanisms in place  
16 and an in-vivo system, physiological conditions to  
17 make us at least more comfortable in making the  
18 decision if that nitroso is negative in the in-vivo  
19 mutation. Ultimately, it is the carcinogenicity, but  
20 we cannot possibly continue with an impurity such as  
21 nitrosamine and go ahead and conduct a  
22 carcinogenicity, a two-year bioassay for every nitroso

1 that has been detected. So, we are trying to be  
2 reasonable and practical and resource-sensitive in  
3 what we ask for, but we also need to make sure that it  
4 is the public safety that is important.

5 DR. HECHT: Well, the first thing to do  
6 is to look at the structure and compare it to the huge  
7 amount of data that we have on structural aspects of  
8 nitrosamine carcinogenicity. You will not find many  
9 negatives.

10 DR. ATRAKCHI: That is correct. That  
11 is the concern.

12 DR. BUCHER: This is John Bucher. I  
13 think that if you are looking at doing an in-vivo  
14 assay after a negative Ames, which I agree is the best  
15 thing to do, I would encourage that there be a  
16 requirement that there be a couple of known  
17 nitrosamines running along with that assay, whatever  
18 that assay might be, so that one could (a) make sure  
19 that that particular assay is picking up nitrosamines,  
20 and that (b) you have some even imprecise idea of  
21 relative potency.

22 DR. ATRAKCHI: Absolutely. A positive

1 control of one of the nitrosamines, which likely would  
2 be NDMA or NDEA would be run in parallel in the same  
3 test. Anyone else from FDA who would like to comment  
4 on this or add to this question that I know we all are  
5 interested in having a discussion over?

6 DR. MCGOVERN: This is Tim McGovern  
7 from FDA. I'll just ask -- and I think it was Dr.  
8 Hecht who mentioned it -- that you are just looking at  
9 the nitrosamine database. There are very few  
10 nitrosamines that test negatively in a carcinogenicity  
11 study. So, I guess I would just ask the question, is  
12 there any concern even should one of these impurities  
13 test negative in an Ames assay or a modified Ames to  
14 some degree and then a followup in-vivo assay, would  
15 you still have any residual concern about its  
16 carcinogenicity potential?

17 DR. HECHT: I think if it was negative  
18 in the Ames and negative in an in-vivo system assay  
19 and you take a good look at the structure compared to  
20 what is known about nitrosamines of similar structure,  
21 I think you would be on solid ground to say that a  
22 particular compound would likely not show carcinogenic



1 activity.

2 DR. ATRAKCHI: Okay. If there are no  
3 further comments on this question, then I think we  
4 will move on to Question 4.

5 Okay. How would the risk assessment  
6 change when multiple nitrosamines are present in a  
7 drug product? What are the key variables to consider  
8 when conducting such risk assessment? One nitrosamine  
9 could be mutagenic carcinogen with another one that is  
10 mutagenic carcinogen and so on. This is not an  
11 unlikely scenario unfortunately. More than one  
12 nitrosamine has been detected recently in a single  
13 drug substance and/or drug product. Would the risk be  
14 additive or synergistic. Do we know how the in-vivo  
15 PK or pharmacokinetics would change when we have  
16 multiple nitrosamines in the same drug product or drug  
17 substance? What is the efficiency of the DNA repair  
18 to handle multiple nitrosamines at the same time and  
19 considering all of the other sources of nitrosamines  
20 together? I would like to start with Dr. DiNovi.

21 DR. DINOVI: Thank you. As with the  
22 questions we have done so far, this is a very

1 multilevel, multifaceted question. My particular area  
2 of expertise is on the exposure side. I'm the Dietary  
3 Assessor on the Center for Food Safety. And when we  
4 consider I will not say risk assessment since  
5 certainly substances added to food are not supposed to  
6 present a risk, but you understand what I mean. When  
7 we are looking a chemically closely related  
8 substances, our default assumption is that the  
9 effects, any toxic effects would be additive. And the  
10 way we deal with that is simply do the exposure in a  
11 way of simply adding the materials. More to the point  
12 of the nitrosamines here, though, there are classes  
13 that come back to my mind, where the structures  
14 present different toxicities, and what our  
15 toxicologists have done as have others around the  
16 world is taken toxic equivalent factors into effect.  
17 So, the way you deal with it in the assessment, of  
18 course, is you look at the exposures and you weight  
19 the exposures based on the relative toxicities. It is  
20 fairly straightforward and fairly simplistic, but we  
21 are also not looking at situations with carcinogens  
22 typically. These are in fact, but you are not looking

1 at the kind of questions that we have here where it is  
2 nonmutagenic versus mutagenic. That part of the  
3 answer to this question I am going to have to leave to  
4 our toxicology colleagues, and we can come back if  
5 there are other questions we want to talk about with  
6 the exposure. So, let me just pass it on at this  
7 point. Thank you.

8 DR. ATRAKCHI: Dr. Cronin.

9 DR. CRONIN: Thank you, yes. And I am  
10 going to put a modeling slant to this. So, I think  
11 the previous speaker set me up quite nicely in many  
12 ways because I was going to start off by saying, well,  
13 really repeating the question here. The key  
14 consideration is whether the concentrations, the  
15 potencies are additive and whether we can make an  
16 assumption as we have just heard or what would we need  
17 to assume synergy. I will start off by also passing  
18 the buck on the synergy question. I am not aware of  
19 synergisms specifically in carcinogenicity. As I say,  
20 I will rely on the experimental toxicologists who  
21 determine whether I am right or wrong or whether we  
22 need evidence on that. I guess where that may come in

1 place is if we see things like increased metabolic  
2 activation or knocking out of defense mechanisms. And  
3 again, if we are going to assume that from my  
4 simplistic modeling point of view, if we are assuming  
5 that some of the defense mechanisms are relatively  
6 generic and unspecific, then we can probably assume  
7 additivity. I agree with the first respondent. We  
8 will consider similar structures. We will work  
9 together and beat the additive. But we are assuming  
10 in that the similarity in mechanism, similarity in  
11 potency, and similarity in reactivity. This is quite  
12 possible, but also let us bear in mind the subtleties  
13 of some of the reaction mechanisms, and we know we  
14 have these what we know as activity cliffs when we  
15 have the correct substitution patterns. So, here we  
16 also have a second opportunity to think about  
17 categories and chemicals and when can we lump  
18 together, when can we group together molecules and  
19 understand the problems. And also where do we have  
20 the data. And I am going to discuss data more  
21 tomorrow in the answer to Question 6. But we need to  
22 consider it is not just a question whether we can

1 group together, but do we have data to support any  
2 argument. And also think about the differences. We  
3 are actually getting quite good in some areas. I will  
4 talk again in more detail about read-across tomorrow,  
5 but we are getting quite good at understanding  
6 differences between molecules and what they may  
7 potentially have. Here we can understand them in  
8 terms of reactivity and possibly bioavailability.

9           So, we also need to think about the  
10 mechanisms of action and whether we have information  
11 of mechanisms of action. And we have also been  
12 thinking, wondering what scenario would be if we had  
13 for instance a very high potency carcinogen and  
14 something that may be acting by the same mechanism but  
15 with a much lower potency. There is really a need in  
16 that regard to even include additivity if the  
17 high-potency carcinogen is several orders of magnitude  
18 above that of the low-potency carcinogen. More  
19 specifically around read-across and QSAR. Again, I  
20 will define these terms and talk about them a little  
21 bit more tomorrow. Let us start with QSARs. I am not  
22 aware of an QSARs for mixtures with regard to these

1 particular endpoints. Mixtures related to QSARs tend  
2 to be on the whole the vast majority for acute  
3 toxicity or acute lethality. Where we do see  
4 occasionally additivity on a very occasionally  
5 synergism. In terms of read-across, again read-across  
6 relies on adequate data. So, here would be adequate  
7 data for two or more nitrosamines that we could  
8 extrapolate across to a set of similar compounds. We  
9 will talk about this tomorrow. It is possible. It  
10 has been done. There is some work on read-across for  
11 mixtures, particularly within the UVCB area, but is  
12 really assuming that we can assure ourselves of the  
13 similarity of our structures. So, we are again  
14 getting back to this argument of structural activity,  
15 and we know we have some knowledge in that area.

16           With regard to the question, one area  
17 where we can use SAR and QSAR -- we have just been  
18 having this discussion of course -- is to predict  
19 whether a compound may be mutagenic or may be a  
20 nonmutagenic carcinogen. So, we may be able to take  
21 if we have two or a small number of nitrosamines in  
22 the sample, we may be able to use particular modeling

1 approaches or read-across to enable some kind of  
2 assessment to be made to at least see whether or not  
3 they fit into those categories that are on the screen  
4 there.

5           The other thing I would like to  
6 highlight is the possibility of using some of the  
7 techniques that are currently applied in terms of  
8 commutative risk assessment, particularly commutative  
9 assessment groups. And the European Food Safety  
10 Authority, EFSA, has done a lot of work in this area.  
11 And their work is on residues from pesticides. So,  
12 not nitrosamines but in some ways analogous to what we  
13 are talking about here. So, I think there could be  
14 some learnings from that, and they have a full-stage  
15 methodology based around identification,  
16 characterization, collecting the data, and grouping.  
17 And if you look at their approach, in part of their  
18 approach, they are saying at the lowest level where  
19 you have the least certainty, you can assume we are  
20 looking at some kind of structural similarity or  
21 grouping basis, but we may not know for instance,  
22 mechanisms of action or similar through up to the

1 highest level where we can assure similarity in  
2 mechanisms of action. So, as with many of the  
3 arguments in this workshop that I will put forward, it  
4 comes out to structured activity relationships and  
5 also being clever about what we are doing and learning  
6 and also building up bodies of evidence. And also  
7 thinking about how we can extrapolate what we are  
8 talking about in earlier questions about structural  
9 activity and showing that we are using the same  
10 information and the same groupings, not only for  
11 single chemicals for applying for single chemicals,  
12 but can we use that to apply up to groups of chemicals  
13 that may be present in the same sample. Thank you.

14 DR. ATRAKCHI: Thank you. Dr. Bucher.

15 DR. BUCHER: Yes. So, my answering  
16 this question really relies on the experience that we  
17 have generated over the course of many years looking  
18 at combinations of chemicals in toxicology studies,  
19 and it has really been our experience that  
20 irrespective of the mechanisms in general for these  
21 chemicals, additive models more than adequately  
22 predict outcomes in the vast majority of cases. In



1 particular when you are dealing with chemicals of  
2 similar mechanism as you would think in nitrosamines  
3 and also certainly at the levels of nitrosamines that  
4 would be appearing individually in any of these drugs  
5 at an acceptable intake level, so I do not think it  
6 matters really to my mind. When we do chemical  
7 mixture studies, it does not matter whether they are  
8 mutagenic or not mutagenic, if there is a carcinogenic  
9 potency associated with a particular chemical, those  
10 would be the numbers to use for the acceptable intake  
11 level, and in my mind, it is -- so in my mind, in our  
12 experience, until you get to significant exposure  
13 levels of chemicals, you very rarely will run into  
14 anything that looks like either synergism or  
15 antagonism. So, I think additive models are probably  
16 more than adequate for the cases of nitrosamines that  
17 you are going to be dealing with.

18 DR. ATRAKCHI: Thank you. Dr.  
19 Guttenplan.

20 DR. GUTTENPLAN: Yeah, I basically  
21 agree with the previous comments. The important  
22 factor here is that we are dealing with subthreshold

1 levels with respect to DNA repair. As Dr. Kyrtopoulos  
2 mentioned, even for the saturable enzyme, which is not  
3 really an enzyme but a protein O6-methylguanine  
4 transferase, we are apparently well below the  
5 threshold in almost any organ of the body, and the  
6 levels in drugs is so low that we are probably not  
7 going to approach the threshold. I will say though  
8 that different nitrosamines are going to be repaired  
9 by different enzyme systems. Most of them can be  
10 repaired by the O6-methylguanine transferase system,  
11 but as you get to larger adducts, particularly above  
12 the ethyl group, then there are other base excision  
13 repair and nucleotide excision repair. And they are  
14 all going to play a role, but in each case, if you are  
15 subthreshold, then there is no reason to think that  
16 you are not going to have an additive response for  
17 each agent. So, I basically agree with what has been  
18 said so far.

19 DR. ATRAKCHI: Dr. Adamson.

20 DR. ADAMSON: Generally, within the  
21 same class of compounds, the default position is  
22 generally addition unless there is some indication

1 otherwise. But I would say -- you brought up additive  
2 or synergistic, there is also the possibility of less  
3 than activated, particularly when compounds need to be  
4 activated when you have binding and when you have DNA  
5 repair. But I would say at the low levels that the  
6 nitrosamines are present in a drug product, probably  
7 those do not factor in. You probably would not have  
8 competition for activation. You probably would not  
9 have competition for binding. You probably would not  
10 have competition for DNA repair. So, with regards to  
11 the small amounts that are present in drug products, I  
12 would say that you would probably, unless indicated  
13 otherwise, you would have to do an additive.

14 DR. ATRAKCHI: Thank you. Dr. Hecht.

15 DR. HECHT: Yes. I agree. Considering  
16 the low levels that we are going to be observing,  
17 additivity is definitely the default assumption of the  
18 molar amounts that are present. So, I agree with  
19 everything that has been said about additivity.

20 DR. ATRAKCHI: Dr. Rice.

21 DR. RICE: I too agree that additivity  
22 is the most likely way to consider the issue of

1 multiple carcinogens. I would think though that there  
2 is always the likelihood that if there is more than  
3 one nitrosamine in a product, it could well be one  
4 about which next to nothing or absolutely nothing is  
5 known. And I should not think that the regulatory  
6 focus would be to be undertake a full-scale search of  
7 chemical structure to identify precisely what this  
8 unknown nitroso compound is. I should think given the  
9 fact that it is fairly clear that dimethylnitrosamine  
10 or perhaps the most potent of known carcinogens, that  
11 an overall analysis of total nitroso compounds present  
12 in an adduct could -- from the standpoint solely of  
13 other health protection, you could treat them as  
14 essentially an equivalent total dimethylnitrosamine.  
15 Most of the time that will be an overestimate of the  
16 potential hazard, but that is an error on the correct  
17 side of caution. So, in sum, I would just treat them  
18 as additive, and in the case where there is a new  
19 unknown or normally known agent in addition to one of  
20 the better understood nitrosamines or something added  
21 to them as though they were equivalent in the known  
22 publications. Thank you.

1 DR. ATRAKCHI: Thank you. Dr.  
2 Kyrtopoulos.

3 DR. KYRTOPOULOS: Yes, I think Dr. Rice  
4 made an excellent summary of the situation. And I  
5 agree 100 percent with what is being said. Basically,  
6 additivity and if necessary, taking the potency of the  
7 most powerful of the nitrosamines, NDMA. I do not  
8 have anything else to add.

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

11 DR. EISENBRAND: (No response.)

12 DR. ATRAKCHI: We can move to Dr.  
13 Zeiger.

14 DR. EISENBRAND: So, I am back. Sorry.  
15 I had a lot of problem with it. Well, I agree totally  
16 with what has been said concerning additivity. I  
17 think an additive modification be applied here, and it  
18 may be in a case where we have nitrosamines with  
19 vastly efferent biological activity, the most potent  
20 ones and nitrosamine of minor potency, then I would  
21 think that the potent one, of course, would primarily  
22 add and be the one that should be looked at and

1 evaluated. Just to mention, there has been I think it  
2 was in 1990 a publication from the German Cancer  
3 Research Center, the first author I think if I recall  
4 correctly -- I can send you this -- is Pergot [ph]  
5 where they tested combined application in rats of I  
6 think it was diethylnitrosamine or  
7 dimethylnitrosamine, nitrosomorpholine, and  
8 nitrosopyrrolidine, and what they found out in that  
9 lifelong exposure study was clear additivity of the  
10 effects. So, that is published already since many  
11 year.

12 DR. ATRAKCHI: Thank you. Dr. Zeiger.

13 DR. ZEIGER: Okay. I also agree that  
14 additivity is the most appropriate way to go for the  
15 reasons expressed by all of the previous speakers.  
16 Obviously for the data just presented. Just one point  
17 on the question. I would not separate out mutagenic  
18 from weakly mutagenic carcinogens. I agree with the  
19 comments on additivity. Thank you.

20 DR. ATRAKCHI: Thank you, Dr. Zeiger.  
21 I would like to make a comment here. Well, to sum up  
22 this question is basically everybody seems to agree

1 that if we have one nitrosamine as a contaminant, as  
2 an impurity in the drug, will we have five? To be the  
3 most conservative approach is to use the amount of the  
4 most potent nitrosamine and to apply for all the five,  
5 even though there is one or more of the others that  
6 either there is no carcinogenicity data or the data is  
7 very poor. And it seems like almost -- well, actually  
8 all of you agree with this assessment that the risk  
9 assessment would be an additive in using the most  
10 conservative and most potent carcinogen, and  
11 nitrosamine is carcinogenic.

12           Going back a little bit for the whole  
13 day that we have been discussing now, reaching to  
14 Question 4, it would seem to me that all of you have  
15 indicated the large amounts of endogenous formation,  
16 and that is due either internally formed or  
17 exogenously from foods that we are exposed to for  
18 nitrosamines. And the miniscule amount that we could  
19 be exposed to from drugs. I assume you are not saying  
20 or indicating that we do not need to worry about the  
21 small amounts of nitrosamines in our drugs. Is this  
22 accurate? And certainly, that is not the case. It

1 does not seem that is the case based on what we just  
2 discussed in Question 4 where we said if we have one  
3 or more nitrosamine, we need to use the most  
4 conservative limit of the most potent carcinogen, and  
5 use that one as the total for the five or six  
6 nitrosamines in a drug. However, it is not clear to  
7 me that from what we have discussed all day that it is  
8 the endogenous formation, the exposure from exogenous  
9 intake compared to the minimal or the small amount  
10 that has been contaminated in drugs should be an  
11 issue. Is this what you have indicated or not?

12 DR. EISENBRAND: Maybe I comment first,  
13 if you allow.

14 DR. ATRAKCHI: Absolutely.

15 DR. EISENBRAND: Well, you know, as I  
16 pointed out in my lecture, the data on exogenous  
17 exposure first in my opinion are relatively outdated.  
18 So, it is our suspicion, our interpretation of the  
19 data with our approach that the amount that is being  
20 taken in for contaminated drugs by comparison may be  
21 very, very low. But we do not know really for sure.  
22 That is my point. That is why I think we need to



1 update first the database on exogenous, but even more  
2 so the database on endogenous formation of nitroso  
3 compounds. We need really scientifically based  
4 updates on these data because they will become very  
5 important when it comes to risk assessment. And I  
6 mean I just recall the last one of the publications  
7 about ranitidine I show where you have this  
8 publication of 2,016 reporting about substantial  
9 in-vivo formation of nitrosodimethylamine from  
10 ranitidine. We need to look at that. This is a very  
11 relevant question in my opinion still. By and large,  
12 I agree with you that probably we finally can say that  
13 normally the contamination with preformed nitroso  
14 contaminants of drugs is relatively negligible in  
15 comparison to the exogenous exposure for food and even  
16 more so to the endogenous exposure. But we need to  
17 have safe data on that. That is my opinion.

18 DR. ATRAKCHI: I understand that there  
19 are recent studies that came out of the Center for  
20 Foods where they indicate the amounts in foods are  
21 fairly low. The amount of nitrosamines in foods over  
22 the past 20 years is extremely low. So, we need to

1 take that into consideration, and I think Dr. DiNovi  
2 can comment on this.

3 DR. DINOVI: Yeah. It is certainly  
4 less than 1 mcg a day, and that is true for all of the  
5 studies we looked at. One of my colleagues, Dr. Jolie  
6 [ph] just recently went through and did a review of  
7 nitrosamines in food, and that was the conclusion,  
8 less than 1. Even at a high percentile of the  
9 distributions. The thing about what we are talking  
10 about here is precision in a risk assessment is much  
11 more of an academic than a regulatory concern. At  
12 CDER, you need to make timely resource-efficient  
13 decisions, and we really do not have the luxury to go  
14 beyond some of these false assumptions.

15 DR. ATRAKCHI: And also in terms for  
16 drugs, the drugs they have a GMP. They need to be  
17 clean and not containing impurities. So, it becomes  
18 an issue of quality. At the beginning, it is a  
19 quality issue. Then, it comes the safety issue. So,  
20 that is important for us. We cannot allow any  
21 impurity, whether regular impurity or mutagenic  
22 impurity to be above a certain level. That is why we

1 have guidelines. That is why we have regularity  
2 limits on such things, excipients and impurities and  
3 so on. But beyond that, the nitrosamines as we all  
4 know, they have been put in its own class as a cohort  
5 of concern in N7. They need to be much more  
6 restricted below a 0.5 mcg per day because of their  
7 potency as mutagenic carcinogens. So, it just seems  
8 to me that whether it is this study, as you indicated,  
9 Dr. Eisenbrand, the database needs to be updated.  
10 There are some new studies that did show there are  
11 very little amounts of nitrosamines in foods, and the  
12 intake is fairly low. So, I am just trying to make it  
13 clear that none of you is saying that we do not need  
14 to regulate or we do not need to worry too much about  
15 the small amounts of nitrosamines in drugs. I am  
16 assuming that is not what you are saying here.

17 DR. RICE: May I make a comment on  
18 that?

19 DR. ATRAKCHI: Absolutely.

20 DR. RICE: I found in reading the  
21 materials you supplied in preparation for this  
22 workshop, both in the Guidance document and the

1 European Medicine Agency, very brief mention of  
2 laboratory findings that the amount of  
3 dimethylnitrosamine in ranitidine samples tended to  
4 increase over time, and thus could not very well have  
5 come from contaminants arising in the manufacturing  
6 process. If in fact you look at the structure of  
7 ranitidine, which is I suppose fairly remarkable in  
8 that within the molecule there is both a dimethylamino  
9 group and a potentially nitrosating nitroalkene  
10 structure that dimethylnitrosamine may be forming in  
11 the finished drug product as a decomposition product  
12 that tends to increase over time. And I would very  
13 much like to see that suggestion confirmed or refuted  
14 by further studies. If a nitrosamine contaminant  
15 analyzed during decomposition of the active  
16 pharmacologic ingredient, then that renders almost  
17 moot efforts to calculate just how much is derived  
18 from whatever might have been there at the beginning  
19 of packaging or whenever a single sampling was done.  
20 Can you comment from the FDA standpoint on this issue?

21 DR. ATRAKCHI: Yes. I will let Dr.  
22 Keire perhaps can comment on this.

1 DR. KEIRE: Yeah. Sure. I think the  
2 drug has to be stable over its shelf life and keep any  
3 nitrosamines that may be forming over time to a level  
4 that is acceptable. And when we looked at ranitidine  
5 samples over time -- I am talking about months -- that  
6 we observed that the amount of NDMA did increase over  
7 time, and they went above the viable intake limit that  
8 had been set for the drug. Of course, this was part  
9 of the information that was used to make a decision  
10 about requesting market removal of the drug. So, that  
11 is one aspect of it. But I would also mention that  
12 there is a recent publication from the group that  
13 showed that this was very formulation-specific. So,  
14 if you have particular polymorphic forms, amorphous  
15 versus crystalline forms of the drug, you would get  
16 more degradant in one form over another. So, it is  
17 possible, and we also observed this in other, from  
18 product to product, the amount that you would see that  
19 would form over time would be very different. Some  
20 products remain below this 96 nanogram limit for long  
21 periods of time. So, there is a potential that there  
22 are some formulations that could stabilize this drug

1 such that the amount of NDMA would not form  
2 excessively. And I guess the other thing I would like  
3 to comment on is the very valid point brought up by  
4 Dr. Eisenbrand about, you know, these studies that are  
5 about endogenous formation of NDMA in the GI tract,  
6 and I guess where the supposition is that this is  
7 happening, and the FDA is also concerned about that.  
8 And whether there is a clinical trial that has been  
9 performed to look into exactly that point. That has  
10 not been completed yet, but certainly we are very  
11 interested in checking the results. Like you said,  
12 what we really be careful about what we base our  
13 decisions on. We need to have very good data and know  
14 what has been discussed. The scientific literature in  
15 this area is fraught with examples of measurements  
16 gone awry for whatever reason. So, we have to take a  
17 lot of care to measure things down here in the parts  
18 per million and parts per billion range, and certainly  
19 the sample preparation is key. You do not want to  
20 introduce any artifacts in the measurement process  
21 itself. So, I will stop there. Thank you.

22 DR. ATRAKCHI: Thank you, Dr. Keire.

1 Anyone else who would like to comment?

2 DR. ADAMSON: I generally what you say  
3 was correct, but I also agree that we do need some  
4 up-to-date data with increased measurements to see  
5 what endogenous formation of the nitrosamines is. And  
6 I would also like to bring up I remember reading  
7 several years ago a study I think it was by Shubik  
8 where he gave -- I believe the compound was  
9 pipericycline, but I am not positive of that. But I am  
10 probably 90 percent sure. It was formulated with  
11 ascorbic acid N. And therefore nitrosamine was not  
12 formed. But if you checked it out without ascorbic  
13 acid being present, you would be forming in the same  
14 laneu [ph] as in the stomach that could be forming a  
15 nitrosamine. So, I think there is something positive  
16 to consider formulations of some of these drugs with  
17 an antioxidant, like the vitamin E or ascorbic acid or  
18 something else. And I think also with regards to the  
19 comment that came up with regards to the final  
20 formulation of a drug, it might be interesting to  
21 check out the final formulation, which does or does  
22 not contain an antioxidant to make sure that the drug

1 does not break down to nitrosamine. Thank you.

2 DR. EISENBRAND: Could I comment as  
3 well?

4 DR. ATRAKCHI: Yes, please.

5 DR. EISENBRAND: It is very right what  
6 has been said. This compound, ranitidine, reminds me  
7 very much of aminopyrine, the compound I showed in my  
8 talk where we literally found that this always just  
9 presents a snapshot of dimethylnitrosamine  
10 contamination because you could not predict it because  
11 any time you measure it again, it turned out to be  
12 higher. And Dr. Keire has already alluded to the  
13 problem of these highly reactive materials of avoiding  
14 artifact formation during analysis. This is not  
15 trivial. This is a real problem because one has  
16 really to try everything to show that there is no  
17 artificial formation. But by and large, these  
18 compounds with these structures like aminopyrine or I  
19 think also ranitidine are really very easily reactant.  
20 And that is why I think this potential of in-vivo  
21 formation needs to be really considered thoroughly.  
22 And in a sense putting antioxidants or ascorbic acid



1 into the formulation may be a very good possibility.  
2 But with aminopyrine, we measure this also using  
3 ascorbic acid to inhibit dimethylnitrosamine  
4 formation. And it turned out that the  
5 pharmacokinetics are quite different. For instance,  
6 aminopyrine was recirculated for the gut salivary  
7 glands, reflecting just blood levels, plasma levels.  
8 And ascorbic acid was after the first passage, it was  
9 just done. So, the protective action of vitamin C was  
10 just for the first passage through the  
11 gastrointestinal tract, not for the delayed one when  
12 the drug was recirculated. Maybe it is different with  
13 cimetidine but maybe not. So, that was my comment.

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

16 DR. KEIRE: Yeah. I mean I guess that  
17 each of these drugs is different, and so there is  
18 going to be some case-by-case analysis of the  
19 reactivity of these things and the conditions needed  
20 to get conversion of any particular drug. So, there  
21 is nitrosation chemistry. There is a lot of  
22 literature about it that is quite complicated, and the

1 conditions have to be right to get certain reactions  
2 to go. And so, I think that is another consideration.  
3 But in basic chemistry, there is not the potential for  
4 particularly biologic enzymatic processes that might  
5 lead to formation of nitrosamine.

6 DR. ATRAKCHI: There is a question from  
7 the attendees. I will read it. Nitrosamine exposure  
8 level from foods including water relative to IV drugs,  
9 where IV drugs are not subject to digestion and  
10 absorption. Would anyone like to comment on this?

11 DR. EISENBRAND: Well, my comment would  
12 be that needs to be studied case-by-case. If you give  
13 a drug IV and it is just distributed systemically, it  
14 might very well end by being recirculated like many  
15 drugs where you can even measure blood levels in  
16 saliva. So, it really -- at first it will go through  
17 the gastrointestinal tract. The second point is that  
18 nitrosation may very well occur elsewhere in the body.  
19 As soon as inflammation or infections, it is always  
20 then connected to the generation of nitrogen monoxide  
21 and NOx. And then you have the nitrosating there.  
22 So, irrespective of the way of ingestion.

1 DR. ATRAKCHI: Thank you. Any other  
2 comments on Question 4 from the panelists?

3 I would like to go back to the  
4 biomarkers. We have talked a lot about DNA adducts  
5 and other biomarkers that could be used to determine  
6 risk assessment. Can we elaborate on this a little  
7 bit more? Can we have more discussion on what do you  
8 think about all of biomarkers that you have discussed,  
9 we have discussed today, that could be more  
10 appropriate for nitrosamines?

11 DR. HECHT: I think DNA adducts would  
12 be good to look at. I think that we have the  
13 technology now to reliably quantify DNA adducts by  
14 high-resolution mass spectrometry, and we also have  
15 the knowledge based on years of study about artifact  
16 formation. So, I think with regard to the question of  
17 endogenous formation, which is critical here because  
18 there are really high levels in endogenous formation,  
19 maybe we do not have to be that concerned about the  
20 low levels that are present in drugs. And I think we  
21 could envision experiments similar to what was done  
22 with nitrosoproline 25 years ago by looking at its

1 levels in urine when you gave people proline and  
2 nitrite. You can now envision studies where you can  
3 look at DNA adduct formation from compounds like  
4 dimethylnitrosamine by giving the precursors  
5 dimethylamine perhaps labeled and then determining the  
6 level of DNA out of formation using the labels to  
7 trace it. So, there are ways that you could really  
8 address this question. Dr. Eisenbrand mentioned still  
9 a critical question with respect to the overall  
10 exposure to nitroso compounds.

11 DR. ATRAKCHI: Is it fair to say that  
12 we really understand the mechanism or action of  
13 nitrosamines at this time? Do we really know it is  
14 only O6? Is it combination of O6 and N7 methylation  
15 when we say we can use the biomarkers let us say for  
16 the O6 methylation, would we be confident that this  
17 would address?

18 DR. HECHT: Well, I think we are  
19 confident that DNA damage is critical. I think we are  
20 pretty confident about that. We are reasonable  
21 confident that O6 methylguanine is important in the  
22 case of dimethylnitrosamine. And there is plenty of

1 data on that. But if you were going to look at DNA  
2 adducts, you would not have to restrict your analysis  
3 to O6 methylguanine.

4 DR. ATRAKCHI: Very good thank you.

5 DR. KYRTOPOULOS: May I add something?

6 DR. ATRAKCHI: Of course.

7 DR. KYRTOPOULOS: Certainly,  
8 O6-methylguanine is important, and there is a lot of  
9 experimental evidence from certain animals, directly  
10 modified animals, which clearly demonstrated  
11 carcinogenesis by methylating agents. However, just  
12 because it is the best studied model, we should not  
13 say that it is a general model. Not all nitrosamines  
14 methylate. In fact, I think that for many of them, I  
15 personally do not know which is the most important  
16 kind of DNA damage that they cause. So, DNA adducts  
17 in general -- first of all, I agree absolutely what  
18 was said before by Dr. Hecht regarding the need to  
19 apply modern, powerfully sensitive methodologies,  
20 clinically specific methodologies to the analysis.  
21 And certainly there is a potential today to go down to  
22 very high sensitivities. So, measuring DNA adducts is

1 a good way to have biomarkers of exposure, but if we  
2 want to go a step further in a mechanistic sense  
3 involving biomarkers of risk if you like, like  
4 O6-methylguanine is both a biomarker of exposure but  
5 also a biomarker of risk. We have to know much more  
6 about how the mechanism of carcinogenesis by many of  
7 the nitrosamines, which I do not think we do. Even  
8 for the simple ones. Diethylnitrosamine. Secondly,  
9 O6-methylguanine is important. But O4-arylamines  
10 [ph] probably plays a role in some cases. In fact, if  
11 know the correct name -- it is a long time since I  
12 read this literature. I think O4-arylamines [ph]  
13 was accumulated. So, it could be that there are  
14 different adducts playing an important role in  
15 carcinogenesis by different nitrosamines. From what I  
16 am aware, we do not really know which are the key  
17 adducts. So, we cannot really say today that we know  
18 enough to develop risk biomarkers. DNA adducts is not  
19 exposure, quantitative exposure, or even just to  
20 verify that there is exposure. It is certainly  
21 important, and it is achievable today. That's all.

22 DR. ATRAKCHI: Thank you. So, you're

1 saying that essentially, we should not limit ourselves  
2 to only the 06-methylation, although for NDMA and for  
3 the nitrosamines that are well studied, we know that.  
4 We know that very well. A lot of studies have been  
5 done and shown that, but we should not be limited to  
6 only the 06 as our biomarker for exposure.

7 DR. KYRTOPOULOS: Yes, I think so. I  
8 mean the fact that NDMA is a problem in the context  
9 that we are discussing, the drugs. And it is a very  
10 powerful carcinogen. So, 06-methylguanine is  
11 certainly relevant to our efforts to evaluate the  
12 problem that this NDMA contamination poses, but I dare  
13 say, I would not generalize the importance of  
14 06-methylguanine.

15 DR. ATRAKCHI: Thank you. I would like  
16 to ask my colleagues from FDA if they have any  
17 comments or if they have received any questions from  
18 the FNDs because I do not see any at this time.

19 DR. KEIRE: I guess I just have one  
20 comment. I think that there is a lot of DNA around,  
21 right? If you have a meal of fish -- I was just  
22 reading this -- there can be up to like 40 mg of DNA

1 in a meal. And certainly if there are conditions that  
2 are conducive to a nitrosamine formation, there is a  
3 substrate there pretty much all the time for it to  
4 happen. So, I guess it goes back to that conversation  
5 about what potential endogenous sources. And if the  
6 conditions are appropriate for formation of a lot NDMA  
7 from dimethylamine, which is a much simpler substrate  
8 than many of these drugs. Just a comment.

9 DR. ATRAKCHI: Thank you.

10 DR. GUTTENPLAN: I have a comment. In  
11 the publication with ranitidine, they monitored  
12 dimethylnitrosamine in the urine, but they also  
13 monitored total nitrosamines. So, is urinary analysis  
14 a possibility because this could be done in humans, in  
15 human volunteers who are taking the drugs anyhow.  
16 Just a question.

17 DR. KEIRE: Yeah, that is exactly  
18 right. The FDA actually conducted a small trial, and  
19 the results are now pending. So, hopefully, we will  
20 have new data on it to share on that soon on exactly  
21 that question.

22 DR. KYRTOPOULOS: May I add a question



1 to this? One thing that puzzles me about the paper is  
2 the following. I've seen few data on the levels of  
3 dimethylnitrosamine that have been found in drugs.  
4 The first analysis on ranitidine, the amount of NDMA  
5 that were found were enormous. I think it was 2 or 3  
6 mg per tablet. Is that a real finding, or was it  
7 maybe an artifact because subsequent numbers were much  
8 lower. Because if that was the real level that  
9 present in the tablets that were taken by the  
10 volunteers who had these high levels in their urine,  
11 it might even be that they were actually taking it --

12 DR. KEIRE: Right. So those  
13 measurements were done by using a technique called  
14 headspace UCMF that using high temperature to  
15 vulcanize the sample for analysis. And ranitidine is  
16 temperature sensitive. I will form NDMA. So, those  
17 original reports of 3 mg quantities from ranitidine  
18 are not effective measurements, and we were speaking  
19 to that point earlier that you really have to be  
20 carefully how make your measurements on. Sometimes  
21 these compounds -- you know, and actually that was an  
22 FDA method that they used that was developed for

1 valsartan. So, it was developed for a different  
2 drugs, which was not heat labile, and they applied it  
3 to ranitidine and unfortunately, that led to this  
4 artifactual finding. So, what the FDA reports on its  
5 website are much lower numbers, still unacceptable  
6 numbers, but in terms of limits that are set right  
7 now, but much, much, much lower than was in those  
8 original reports.

9 DR. GUTTENPLAN: I believe they  
10 published the correction. The group that published  
11 the ranitidine they published a correction taking into  
12 account the head-space formation, and it was very  
13 minor. It was not a major artifact.

14 DR. KEIRE: So, I'm talking  
15 about -- there are two different things. So, there  
16 was a report by this private lab that reported these  
17 3 mg amounts being formed. But you are correct in the  
18 Zang and Mitch [ph], they did work to see what  
19 percentage of the total from the measurements they  
20 did. It was only 5 percent formed of these large  
21 amounts that they were seeing was formed from the  
22 headspace. You have seen this method in their

1 application of it. But in the other application that  
2 was reported were these really very high amounts  
3 reported. That was just because of the headspace  
4 method used. So, two different things were being  
5 discussed.

6 DR. GUTTENPLAN: Okay. That's clear.  
7 Yeah.

8 DR. ATRAKCHI: Thank you. I cannot  
9 follow the questions on the side. They are moving on  
10 me very fast. But I would like to ask one question  
11 going back to Question 2 on the classification, and  
12 then maybe I will ask my colleagues to read some of  
13 those questions on the side. They disappear quickly  
14 from the chatroom.

15 In terms of the classification, EMA had  
16 come up with one value, one class, a specific number,  
17 which is 18 nanograms per day. Would that be  
18 something that you treat all the nitrosamines as  
19 impurities with one number, and that is lower than the  
20 most potent nitrosamine, NDEA, which we have listed as  
21 an acceptable intake of 26.5. Is that something that  
22 you would consider? Anyone on the panel?

1 DR. EISENBRAND: May I?

2 DR. ATRAKCHI: Yes, please.

3 DR. EISENBRAND: Actually, I wouldn't  
4 really think there is a big difference between 18 and  
5 26. In terms of biological efficacy, it is the same  
6 ballpark more or less. So, these default values of  
7 extrapolation of potential acceptable mutates in my  
8 opinion are helpful and could be used as a primary  
9 measure to protect actually the consumers, but in fact  
10 we need scientific confirmation of this. And this, I  
11 think I come always back to the proposal that one  
12 should really look into what happens outside in the  
13 real world, which, in my opinion, is just what we need  
14 necessarily to take up with foods. And admittedly as  
15 we discussed before, this is low. It is below 1 mcg a  
16 day, internationally even. But by comparison to the  
17 exposure to the potential exposure for contaminated  
18 drugs, it is still higher, much higher in most cases.  
19 I do not know of all of the cases, because this is a  
20 problem that rapidly develops. Many things I just do  
21 not know. I am not aware of. But as a pragmatic  
22 proposal, I think this is definitely in my opinion a

1 rationale to go on and pursue what is happening  
2 outside the drug situation to compare with. It is  
3 more or less the levels of nutritional uptake of at  
4 least -- it is below 0.3 mcg per day. There is at  
5 least a good orientation.

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

8 DR. CRONIN: Yes, maybe if can just add  
9 a thought. I certainly agree it is a starting place.  
10 And we have heard the arguments for that. Clearly,  
11 you may look for evidence and go to a higher level if  
12 such evidence exists. I am certainly aware of some  
13 work from Kevin Cross who recently presented some  
14 information that suggested that you can use SAR and  
15 read-across. We will talk more about this tomorrow.  
16 In some circumstances, we can do read-across and  
17 demonstrate the very high probability that you could  
18 go to a higher level. So, that is how I would view  
19 it, that if you had no other data or information, then  
20 you would start there. Then start to build your lines  
21 of evidence. And certainly starting with SARs and  
22 looking for similar structures in similarity in terms

1 of mechanisms and seeing whether you could read-across  
2 and whether there was room to increase that in terms  
3 of safety. Thank you.

4 DR. ADAMSON: I would like to bring up  
5 one factor that has just been touched on, and that is  
6 are there sensitive populations. For example,  
7 ranitidine was in a syrup that was used primarily for  
8 children and infants. Are there other examples where  
9 there is potential nitrosamines in such medicines that  
10 would be given to newborns because I think they should  
11 be more classified as perhaps more prone to develop  
12 adverse effects than adults.

13 DR. ATRAKCHI: Are you suggesting that  
14 one number -- let us say it is the 18 nanogram per day  
15 would need -- maybe we would need to apply safety  
16 factors for the more sensitive population because that  
17 is certainly not in ICH M7 because ICH M7 considers  
18 that the values in the assessment is fairly  
19 conservative, that there is no need to add safety  
20 factors for pregnant woman or children or any other  
21 sensitive population.

22 DR. ADAMSON: I am not phrasing the

1 issue. I think it needs to be looked out.

2 DR. ATRAKCHI: Okay. Thank you.

3 I will read this comment or question.

4 I think that the discussion of the Ames test appeared  
5 somewhat contradictory. Could we get some clarify  
6 from Dr. Zeiger's statement that the common LACD  
7 protocol was insufficient and that it needed adapting,  
8 e.g., additional S9 systems, or was the overall  
9 conclusion that even a modified assay would be  
10 insufficient.

11 DR. ZEIGER: I did not mean to imply  
12 that there were problems with the OECD protocol. But  
13 the OECD protocol, you know, allows for a variety of  
14 options. For example, I have seen many labs that do  
15 the Ames test with 5 percent S9 as an example. This  
16 is acceptable within the OECD protocol. Yet something  
17 like dimethyl- and diethylnitrosamine need much higher  
18 levels of S9 in order to respond to the assay. This  
19 is what I mean. FDA OECD protocol limits the strains  
20 that are used for testing. There are other strains  
21 that will be positive, whereas these strains might be  
22 negative. The OECD assay protocol emphasizes the rat

1 S9. I think there is more than enough data to show  
2 that other S9s, other rodent S9s, are more suitable  
3 for nitrosamines than rat S9. So, if I got a negative  
4 for a very weak response with rat S9, I would  
5 immediately go to the mouse S9, which might be much  
6 better or hamster S9. Or a higher concentration of  
7 S9. These would still be allowed within the OECD  
8 protocol, but most laboratories will not do this in  
9 general. I would not do it if I was looking at  
10 polycyclic aromatic hydrocarbon, but I would do it if  
11 I was looking at a nitrosamine that came up equivocal  
12 or negative.

13 DR. ATRAKCHI: Thank you. I agree.  
14 There is a great deal of literature out there to show  
15 that the rat S9 may not be sensitive to the  
16 nitrosamines, and some modification in the test system  
17 in the Ames needs to be conducted in order to provide  
18 the more appropriate response.

19 The other comment or question. I do  
20 not think the panel answered this part of the Ames  
21 discussion. If an Ames assay is not considered  
22 conclusive, then why would not the panel recommend



1 going directly to an in-vivo assay directly? Anyone  
2 would like to answer this

3 DR. GUTTENPLAN: Yeah, because it would  
4 be too resource consuming. It is a lot more work and  
5 probably orders of magnitude more expensive. So, if  
6 you can already find a positive in the Ames assay, you  
7 do not have to go ahead to the in-vivo assays.

8 DR. ATRAKCHI: You are correct.

9 DR. ZEIGER: Based on the available  
10 data, a negative in-vivo assay does not counteract the  
11 positive Ames assay. They have many chemicals other  
12 than nitrosamines that are strongly positive in Ames  
13 tests but negative in in-vivo, but gets still negative  
14 in carcinogenicity. Well, it is still positive, I am  
15 sorry, in carcinogenicity. So, if you have a positive  
16 Ames test, no other test really negates the  
17 implications for carcinogenicity of that positive Ames  
18 test, no other gene tox test that we know of.

19 DR. ATRAKCHI: Very good. Thank you.

20 What are the possible reasons a  
21 negative Ames test when it is positive in the in-vivo?

22 DR. ZEIGER: Well, the Ames test does

1 not detect every type of DNA interaction, every type  
2 of DNA damage. The Ames test will not detect DNA  
3 deletions, which might still allow survival of the  
4 cells. But the in-vivo tests look at different  
5 endpoints, the same endpoint but different target  
6 sites and have different sensitivities. So, something  
7 like the new Pig-a test -- that is a gene mutation  
8 measurement in blood cells -- will detect deletions,  
9 whereas as an Ames test will not detect deletions.  
10 The Ames test does not detect all possible DNA  
11 damages.

12 DR. ATRAKCHI: Thank you.

13 DR. GUTTENPLAN: There are compounds  
14 that are just not metabolizing well enough in the Ames  
15 test but are metabolized more efficiently in-vivo, so  
16 you will get a positive result in-vivo. I think  
17 something like diethanolamine will probably not be  
18 positive in the Ames test, but I will bet under the  
19 right conditions, it will be carcinogenic and  
20 mutagenic in-vivo because there is more metabolic  
21 capacity. Many, many years ago people were doing  
22 host-mediated assays, and there were compounds that

1 were negative in Ames test but were positive in the  
2 host-mediated assay. The reason was in the  
3 host-mediated assay where you injected the bacteria  
4 into the tail vein of the animal and then recovered  
5 the bacteria, you had the whole liver metabolizing the  
6 carcinogen. So, that is another reason why the Ames  
7 test does not always detect a potential mutagen is  
8 there just is not sufficient metabolic capacity.

9 DR. ZEIGER: Yeah. I would like to  
10 support that point. In the Ames test, we are just  
11 looking at the metabolic capability of a liver  
12 homogenate supplemented with NADPH, whereas as was  
13 just said, in the animal you have the intact liver and  
14 other organs doing the metabolism. Though, I would  
15 walk back the statement on the host-mediated assay.  
16 That is the assay that got me involved in this deal.  
17 Then, my Ph.D. dissertation was on the host-mediated  
18 assay in nitrosamines. In theory, it is a very  
19 sensitive test. In practice, it is a very insensitive  
20 test because it is measuring mutation in bacteria in  
21 the peritoneal cavity of the animal, which means for  
22 something DMN or diethylnitrosamine, the active

1 metabolite actually had to get into the peritoneal  
2 cavity to deal with the bacteria, so you are working  
3 with a very low level of active product, and very few  
4 chemicals were mutagenic in the host-mediated assay,  
5 except for some of the cyclic nitrosamines.

6 DR. EISENBRAND: May I just comment for  
7 second on the data because it was just mentioned by  
8 Dr. Guttenplan. In diethylnitrosamine is a medium  
9 potency carcinogen, by far not as potent as NDEA for  
10 instance. And we have investigated the mutagenicity  
11 response to the Ames test. First of all, it was not  
12 really active, but it became active when it was  
13 activated with alcohol dehydrogenase. And this was  
14 published years ago. But later on, they also found  
15 that is activated by alpha-C hydroxylation. So, we  
16 have both activation processes. One is the beta  
17 oxidation of the OH group or groups, and the other one  
18 is the still ongoing alpha-C hydroxylation that  
19 finally turns the compound into a DNA alkylating agent  
20 with a positive mutagenicity test.

21 DR. ATRAKCHI: Any other comment on  
22 this?

1           Okay. I would like to go back to the  
2 use of TD50 versus the BNDL. Could we have more  
3 discussion on the pros and cons of each? It seems  
4 like the tendency was more preferable for the BNDL.

5           DR. BUCHER: This is John Bucher. I  
6 can address that. So, the main difference is the BNDL  
7 uses dose response information, whereas the TD50 uses  
8 a point estimate to extrapolate to a particular risk  
9 level. Anytime you are dealing more doses, you are  
10 dealing with better precision as to a lower dose  
11 estimate of risk. But the problem is that the  
12 calculations require multiple dose groups, and for the  
13 nitrosamines, there are many nitrosamines in the TD50  
14 or the carcinogenic potency database that perhaps do  
15 not have this kind of information, and certainly the  
16 calculation for BNDL have not been performed on the  
17 original data. So, I do not think anybody is arguing  
18 that the BND is less preferable than the TD50, but it  
19 is just sort of a practical matter of what is  
20 available.

21           DR. ATRAKCHI: So, you would use either  
22 one?

1 DR. BUCHER: Preferably, I use the BND  
2 if it is available.

3 DR. ATRAKCHI: Okay. Another other  
4 comment?

5 DR. ADAMSON: I agree with John on  
6 this. If it is available, the TD50 is sort of a  
7 default. But I you do not have a dose response.

8 DR. EISENBRAND: Yes. I would also  
9 largely agree. I think the BNDL is preferable  
10 wherever applicable. Do not forget one could  
11 read-across to make the argument that a compound that  
12 has not the right data density still could be  
13 evaluated in that sense if it is close to the  
14 reference compound in structure that may be in TD50.

15 DR. ATRAKCHI: Thank you.

16 A question from attendees. If some  
17 nitroso impurity is unavoidable and it comes negative  
18 for mutagenicity in Ames, will in-vivo assay need to  
19 be conducted to follow up with an in-vivo Comet assay  
20 or a Pig-A mutation assay or transgenic mutation  
21 assay?

22 DR. ZEIGER: Well, my choice would be

1 to follow it up with the in-vivo Comet assay looking  
2 at a number of different tissues and the Pig-A  
3 mutation assay in-vivo. The in-vivo mutation assay is  
4 extensive. It takes a lot of time, and we have data  
5 from other chemicals that the tissues in which you see  
6 mutation are not necessarily the tissues in which you  
7 see tumors. So, other than the liver, you may be  
8 guessing at which tissues to sample, whereas with the  
9 Comet assay, you can sample many tissues at minimal  
10 additional cost. And it takes less time.

11 DR. ATRAKCHI: Right. And certainly  
12 with the Ames, we are addressing an endpoint of  
13 mutation, and the in-vivo test would need to have a  
14 similar endpoint.

15 UNIDENTIFIED PANELIST: We have done  
16 some work on the Pig-A assay with nitrosomethyl- and  
17 nitrosoethylurea and aromatic hydrocarbons. We have  
18 not found it more sensitive than the in-vivo  
19 mutagenesis assay. I guess it is less expensive  
20 because you do not need transgenic animals. On the  
21 other hand, with the in-vivo assay, a lot of the  
22 expense is the animals. They are very expensive, but

1 once you have the animal, then you can sample any  
2 organ you want, and that is not much more expensive.  
3 So, once you get around the cost of treating the  
4 animals, then the assay is not that expensive, but it  
5 is the animal part and treating the animals. But you  
6 have that with any in-vivo assay that you have to  
7 treat the animals, and you have animal costs.

8 DR. ATRAKCHI: Thank you.

9 Another question is, when extrapolating  
10 from one nitrosamine to another, should molecular  
11 weight of the nitrosamine be a factor? The default  
12 limit of 18 nanograms per day or 26.5 nanograms per  
13 day was derived for relatively low molecular weight  
14 nitrosamine. Would higher limits be appropriate for  
15 higher molecular weight nitrosamines?

16 Would anyone from the panel like to  
17 answer this?

18 DR. EISENBRAND: I may just mention  
19 drawing the attention to let us say asymmetrically  
20 substituted methyl long chain where you have quite a  
21 spacing in molecular weight. These compounds are  
22 subject to chain shortening metabolism from the end,



1 from the long end chain here, very similar to the  
2 fatty acid metabolism, so they end up with a common  
3 determinant finally, which is a ketocarboxylate  
4 derivate that methylates again. So, I do not think it  
5 is probably a very good idea to use the molecular  
6 weight information for evaluation in comparison to  
7 dimethylnitrosamine. We have a lot of different  
8 nitrosamines. Dimethyl, diethyl, nitrosomorpholine.  
9 Different rates but similar potency. And as I said,  
10 with the long chain ones, you finally get to a very  
11 short chain methylating analog. So, I do not think it  
12 is probably advisable.

13 UNIDENTIFIED PANELIST: I do not know,  
14 but you may want to on a molar basis. I think that  
15 would be a more reasonable way to make the comparison.

16 DR. ATRAKCHI: But it would appear that  
17 most of the nitrosamines that have been detected are  
18 of the low molecular weight nitrosamines.

19 UNIDENTIFIED PANELIST: Yeah, that is  
20 true.

21 DR. ATRAKCHI: Any other comments from  
22 any of the panelists, from my FDA colleagues on any of

1 the topics that we have discussed today to this point?  
2 Any other questions from the FNDs that I may have  
3 missed?

4 DR. KEIRE: I guess I just kind of have  
5 what may be a naïve question. My lack of familiarity  
6 with this. I guess I have heard that the larger the  
7 nitrosamine is, right. So, you have NMDA, small  
8 molecules, but then when you get to say a drug  
9 substance that may be nitrosylated, so larger, 500  
10 molecular weight maybe because of the other steric  
11 factors, that the larger nitrosamine would be less  
12 likely to be mutagenic or carcinogenic. Is that true?  
13 Can you make that statement?

14 DR. HECHT: I do not think so. I would  
15 be very cautious about making a statement like that.  
16 We can compare for example dimethylnitrosamine with  
17 NMK with much higher weight and also more  
18 carcinogenic. I do not think we can make that kind of  
19 generalization.

20 DR. KEIRE: Okay. Thank you.

21 DR. GUTTENPLAN: I agree with Steve  
22 Hecht on that. Dimethylnitrosamines are potent in the

1 liver but dibutyl nitrosamine is very potent in the  
2 urinary bladder. And it is much larger.

3 DR. ATRAKCHI: Well, I think maybe the  
4 tendency for such a larger molecule like what Dr.  
5 Keire was discussing is that it may come up to be  
6 negative in an Ames test based on the probable steric  
7 hindrance, or it is just going through the bacterial  
8 cell wall and will not cause the mutation. So, right  
9 there up front, the test would be negative for such  
10 larger molecules. But your response is that you will  
11 not just because it is a large molecule, it does not  
12 mean it is not carcinogenic or mutagenic.

13 DR. HECHT: Correct. Just look at the  
14 database. I mean look at the literature. Look at the  
15 papers that Gerhard cited. I mean there are plenty of  
16 relatively high molecular weight nitrosamines that are  
17 highly active carcinogens.

18 DR. GUTTENPLAN: And these might be  
19 good examples of compounds that are not mutagenic in  
20 the Ames but would be mutagenic in in-vivo assays.

21 DR. ZEIGER: Well, so far as I know,  
22 many of these larger molecules are mutagenic in the

1 Ames test. I do not think you can make that  
2 generalization.

3 DR. ATRAKCHI: Very good. Thank you.  
4 Any other comments from anyone on the panel? Hearing  
5 none, I think we are short of five minutes to ending  
6 the first day of the workshop. If there is nothing  
7 else, I would like to thank the panelists for your  
8 valuable discussions, and we will resume tomorrow for  
9 the second and last day of this workshop with the  
10 continuation of the questions. We will get into the  
11 chemistry and the manufacturing of nitrosamines, and  
12 we will start again at nine o'clock. Thank you very  
13 much. Thanks for everybody.

14 (Whereupon, the meeting concluded at  
15 2:41 p.m.)

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CERTIFICATE OF NOTARY PUBLIC

I, IRENE GRAY, the officer before whom the foregoing proceedings were taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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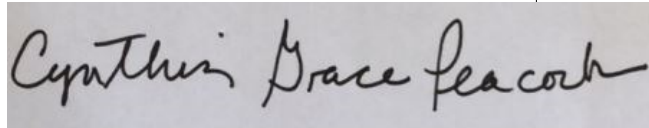
IRENE GRAY

Notary Public in and for the  
District of Columbia

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CYNTHIA GRACE PEACOCK

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