UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA, Plaintiff, v. PHILIP MORRIS USA INC., f/k/a PHILIP MORRIS INC., *et al.*, Defendants.	Civil No. 99-CV-02496 (GK) Next scheduled court appearance: September 21, 2004

UNITED STATES' WRITTEN DIRECT EXAMINATION OF

DR. JONATHAN M. SAMET

VOLUME II

Q: Turning to U.S. Exhibit 17158 (JS057) entitled, "Relative Risk of Coronary Heart Disease by Cigarettes Smoked per Day, Current Smokers versus Never Smokers: Men," can you explain to the Court what the lines and dots represent on this graph?

A: As in previous, similar graphs like this, each line is the findings of one epidemiological study. The points on the lines were plotted out for the persons who have smoked different numbers of cigarettes per day. These relative risk values for those studies with the individual points have just been connected by lines.

Q: Does this graph demonstrate a discernable pattern, doctor?

A: The general pattern is one of rising relative risk for coronary heart disease in men as the number of cigarettes smoked per day increases.

Q: Directing your attention to U.S. Exhibit 17165 (JS071), entitled, "Relative Risk of Coronary Heart Disease, Current Smokers versus Never Smokers: Women," are the studies that are depicted in this graph among the published scientific literature that you reviewed as part of your investigation in this case?

A: Yes, they are.

Q: What does this graph show?

A: Like U.S. Exhibit 17137 (JS033) regarding lung cancer relative risks for women, this graph shows the relative risks in different epidemiological studies for CHD in women, comparing current smokers to never smokers. The graph shows the results of a number of different studies done from the 1960's on. The risk for never smokers is by definition set to one and the Court can see the findings of all these studies showing the increased relative risk of CHD for women over almost forty years.

Q: Turning to U.S. Exhibit 17159 (JS057.1) entitled, "Relative Risk of Coronary Heart Disease by Cigarettes Smoked per Day, Current Smokers vs. Never Smokers: Women," can you explain to the Court what the lines and dots represent on this graph?

A: As in previous, similar graphs like this, each line gives the findings of one epidemiological study. The points on the lines were plotted out for the persons who have smoked different numbers of cigarettes per day. These relative risk values for those studies with the individual points have just been connected by lines.

Q: What pattern can the Court see on this graph, doctor?

A: The general pattern is one of rising relative risk for coronary heart disease in women as the number of cigarettes smoked per day increases.

Q: Why was a different scale used for women?

A: The range of relative risks tends to go to higher levels in women.

Q: Why?

A: Smoking is a more powerful risk factor in women, particularly younger women, compared to men of the same age. This may reflect the differing contributions of other risk factors in men and women.

Q: What are the specific values at the top right-hand corner of each graph on U.S. Exhibit 17159 (JS057.1)?

A: These are values so high as to be off the scale. For example, at the far right there is a value of 22.0 for women in one study who smoke more than two packs of cigarettes per day.

Q: Doctor Samet, looking at the specificity causality criterion that is listed on U.S. Exhibit 17133 (JS031), based on your review of the evidence, has that criterion been met?

A: For coronary heart disease, there is no doubt that there are other causes of coronary heart disease besides smoking. For example, some of those causes include having high blood pressure, diabetes, or high blood cholesterol levels. Specificity is not applicable; there are other causes of CHD in addition to smoking.

Q: Are there studies that have controlled for the other recognized risk factors in estimating the effect of smoking?

A: Yes. In looking at the effects of smoking and causing coronary heart disease, there are a number of studies, for example, the Framingham study and the Nurses' Health Study, where these factors have been controlled, and the effects of smoking on CHD relative risk have been isolated from any confounding and measured.

Q: Doctor Samet, returning to U.S. Exhibit 17131 (JS028.2), which summarizes the Nurses' Health Study, is this one of the studies to which you just referred?

A: Yes, it is.

Q: Did you list the risk factors that were controlled for in that study at the bottom of U.S. Exhibit 17131 (JS028.2)?

A: Yes, that's correct. The risk factors include age and historical time period, Quetelet's index (the same as BMI, an index of obesity), menopausal status, hormone replacement therapy, family history of myocardial infarction, that is, heart attack, and personal history of diabetes, hypertension and hypercholesterolemia.

Q: When those factors are controlled for, what is the effect of smoking?

A: The Court can see looking at the bottom of the table on the right where it says "Adjusted" with an asterisk that when those factors were controlled for in this study, there is a strong dose-response relationship between smoking and CHD. For example, for the never smokers, zero

cigarettes per day, relative risk is one; at one to 14 cigarettes per day, the relative risk increases to 2.3, about a doubling of the risk; 15 to 24 cigarettes per day, about a pack a day, an almost five-fold increase or 500 percent increase in risk for CHD; and, finally for those smoking 25 or more cigarettes a day, a relative risk value of about six.

With regard to whether this effect could be due to other factors, the Court can compare the row stating the relative risk values without controlling for other causes with the values in the row where the other factors were taken into account. A comparison of the two rows demonstrates essentially no changes in the relative risk and no change in the general dose-response pattern.

Q: Doctor, let's discuss the fourth Surgeon General's causal criterion on U.S. Exhibit 17133 (JS031) which is temporality. Is that criterion met by the evidence that you have reviewed for the Court?

A: Yes, that criterion is met. CHD, like the other diseases that we have been discussing, typically occurs at older ages, like lung cancer and COPD. Some people have heart attacks in their thirties and forties, but scientists know that smoking has usually gone on for a number of years before smokers develop CHD. Additionally, smoking has some immediate adverse effects that increase risk for heart attack. Usually, the incidence of CHD arises in the late thirties onward. Typically there has been a substantial amount of smoking before the disease occurs so that temporality is met by the evidence.

Q: Let's discuss the Surgeon General's last criterion, coherence. Has that causal criterion been met by the evidence you have reviewed for the Court?

A: Yes. We have evidence of coherence from a number of lines of research, what happens when smokers quit, some of our information on the effects of smoking on physiological systems

of the body, and the fact that smoking acts to increase the relative risk of developing the disease. There are also data on reduction in relative risk if smokers quit, after they have had a heart attack.

Q: Directing your attention, doctor, to U.S. Exhibit 17160 (JS058), entitled "Relative Risk of Coronary Heart Disease by Number of Years Since Quitting Smoking, Former Smokers Versus Never Smokers: Men" what is the horizontal axis of the graph?

A: As in U.S. Exhibit 17141 (JS037) regarding lung cancer, the horizontal X axis is the number of years quit smoking. By that I refer to the number of years since a smoker has quit and remained a non-smoker. For example, the five means that someone used to smoke, but in the particular study had quit smoking for five years.

Q: The vertical Y axis on the graph goes up to 4.0. What does that represent?

A: The vertical Y axis is the relative risk of CHD. Never smokers are one by definition.

Q: What does each line and dot represent on the graph?

A: Each line represents the results of one epidemiological study, and the dots correspond to the specific data points in the study.

Q: What pattern does the graph establish, doctor?

A: There is a general pattern of declining risk of CHD for men after they stop smoking.

Q: Directing your attention, doctor, to U.S. Exhibit (probably17204) (JS058.1), entitled "Relative Risk of Coronary Heart Disease by Number of Years Since Quitting Smoking, Former Smokers versus Never Smokers: Women," what is the horizontal axis of the graph?

A: As in previous exhibits, the horizontal X axis is the number of years quit smoking. By that I refer to the number of years since a smoker has quit and remained a non-smoker. For

example, the five means that someone used to smoke, but in the particular study had quit smoking for five years.

Q: The vertical Y axis on the graph goes up to 4.0, what does that represent?

A: The vertical Y axis is the relative risk of CHD. Never smokers are one by definition.

Q: What does each line and dot represent on the graph?

A: Each line represents the results of one epidemiological study, and the dots correspond to the specific data points in the study.

Q: What does the graph depict, doctor?

A: There is a general pattern of declining risk of CHD for women after they stop smoking.

Q: What, if any, health benefit is there from smoking cessation with respect to the risk for CHD?

A: There is a relatively immediate benefit within the first year of quitting, and then over time, perhaps within the first five to 10 years after stopping, the relative risks continue to drop for former smokers compared to continuing smokers.

There are fewer studies for women than for men, but the general pattern is about the same, a decline in the relative risk for former smokers as the number of years since quitting increases.

Q: What do these data tell us, if anything, with regard to coherence?

A: These data give scientists some insight into how smoking causes CHD. There appear to be some acute adverse effects of smoking. These immediate effects are thought to reflect the increased levels of carbon monoxide in tobacco smoke and its effects on the delivery of oxygen to the blood stream, and perhaps the pharmacologic effects of smoking, that is, nicotine, or

perhaps other agents within tobacco smoke that may increase the risk for rhythm disturbances of the heart.

Smoking also affects blood clotting. The blood of smokers tends to clot more easily than the blood of non-smokers. This happens because smokers have higher levels of one of the proteins that clots in the blood; that protein is called fibrinogen. The stickiness of platelets is also increased. Fibrinogen and the platelets that stick together to make blood clots tend to be stickier in smokers than in non-smokers. Thus, there are immediate effects of smoking: a higher level of carbon monoxide, effects of nicotine on heart rate and risk for disturbances of the heart beat, and the general tendency of the blood to clot more easily, reflecting the consequences of smoking for elements of the blood clotting system.

Q: With respect to the Surgeon General's causal criteria set out in U.S. Exhibit 17133 (JS031), which of these criteria have been met with respect to coronary heart disease?

A: There is very consistent evidence of increased risk across many studies of coronary heart disease in smokers. The Court has seen that the association varies in strength. The association is somewhat weaker in men than in women, but rising up to relative risk values in the range of two to 10. The Court has also seen the dose-response relationship, showing increasing risk with increasing numbers of cigarettes smoked each day by smokers.

With regard to the criterion of specificity, coronary heart disease does have causes other than smoking, so that criterion is not relevant.

Temporality is met. It takes some years of smoking before the increased risk of CHD occurs.

Finally with regard to coherence, the Court has seen the substantial body of evidence on what happens after people quit smoking and remain non-smokers, the risks decline as do many of

the effects of smoking on the different mechanistic pathways by which coronary heart disease is caused by smoking. Thus, the criterion of coherence has been adequately met.

Q: Doctor, when did the Surgeon General of the United States first conclude that smoking is a cause of CHD?

A: There was a causal conclusion in 1979. CHD cancer was first addressed in 1964, and the report stated, "It is also prudent to assume that the established association between cigarette smoking and coronary disease has causative meaning than to suspend judgment until no uncertainty remains." If the Court looks at U.S. Exhibit 17185 (JS046I), the Court can see a summary of the Surgeon General's conclusions with regard to CHD from 1964 to 2004.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes coronary heart disease?

A: Yes, smoking causes coronary heart disease.

Q: Let's turn now to stroke. What is a stroke?

A: Stroke may also be referred to as cerebrovascular disease. The Court should think of stroke as similar to a heart attack affecting the brain. A stroke occurs when the delivery of oxygen/nutrients to the brain is inadequate. If this happens on a temporary basis, there may be what is called a transient ischemic attack or TIA. A TIA is similar to angina, except now the organ that's being affected is the brain and not the heart.

A stroke involves the death of some of the brain tissue, the brain cells. That may occur because there has been a blockage of blood into that area of the brain as a result of the narrowing of blood vessels, just as I discussed with the coronary arteries. The narrowing may result in the formation of a blood clot on the area of thickening with blockage of the blood supply to that part of the brain downstream from the artery. Some strokes occur with bleeding into the brain, but the net result is that some brain tissue is damaged. The brain does not regenerate itself like some other organs so the consequences of a stroke depend on how big it is and what part of the brain is affected.

Q: What are the consequences?

A: The effects would depend on which particular part of the brain was affected and which side; the left side of the brain or the right side of the brain, because each side of the brain has different functions.

One unfortunate consequence of stroke, whether on the left side or the right side, is that the areas that deal with the muscles, with their motor control, are affected, and then the stroke victim may end up with weakness in one side of the body or even paralysis in one side of the body. That condition is what physician's call hemiparesis, paralysis, or hemiplegia, weakness.

Speech or vision may be affected if the areas of the brain dealing with speech or vision are affected by the stroke. Higher intellectual functions can also be affected depending on what

part of the brain is involved with the stroke. The consequences of a stroke are quite varied depending on location and severity.

Q: What kinds of treatments are used for stroke?

A: That has varied over time. For example, at the moment the modern therapy is to intervene aggressively and early to try to reduce the extent of damage. But for the victim of the stroke, much of the attention is based on rehabilitation, trying to strengthen weakened arms or legs, retraining people in how to talk, and getting them back on their feet and functioning as well as they can.

Q: You mentioned "aggressive intervention." What do you mean?

A: At the moment physicians have learned that with some aggressive approaches having to do with the blood-clotting system, it may be possible to limit some of the damage initially. But this is a very contemporary approach.

Q: What are some of the procedures that are used, as you put it, to get people back on their feet?

A: This would typically involve rehabilitation, that is, helping people to walk again using various kinds of assistive devices: walkers and canes, for example. Also it typically involves putting them on a program of rehabilitation to strengthen remaining muscles, and to retrain their speech, and so on. The regimen really depends on what the consequences of the stroke were.

Q: Doctor, have you had clinical experience working with nursing home patients?

A: In the past, early in my medical career, I took care of patients discharged from the University Hospital in Albuquerque, New Mexico to nursing homes as part of my professional responsibilities. Many of those patients had suffered strokes and had gone to nursing homes for

rehabilitation, or sometimes just for ongoing care because their needs were just too much to be met in the home.

Also, while caring for patients in the hospital setting, I frequently took care of stroke patients, often needing to discharge them to nursing homes because they needed this rehabilitation or they needed to return to the nursing home environment because they were not functioning well enough to go home. I also often saw them come back to the hospital from the nursing home with the complications of being in the nursing home. Sometimes there were bed sores that had developed, sometimes stroke victims have difficulty swallowing, and pneumonia is often a consequence of having food go into the lung instead of down into the stomach. So I frequently saw patients who went to the nursing home and then came back, sometimes later with a complication and were treated in the hospital and then returned to the nursing home.

Q: In your clinical experience, have you seen patients enter nursing homes because of strokes?

A: Yes.

Q: Did you investigate the published scientific literature regarding the causal relationship of smoking and stroke?

A: Yes.

Q: Doctor, when did the Surgeon General of the United States first conclude that smoking is a cause of stroke?

A: There was a causal conclusion in 1989. Cerebrovascular disease was first addressed in 1967, and the report stated, "Additional evidence strengthens the association between cigarette smoking and cerebrovascular disease, and suggests that some of the same pathogenic (sic) considerations pertinent to coronary heart disease may also apply to cerebrovascular disease." If

the Court looks at U.S. Exhibit 17186 (JS046J), the Court can see a summary of the Surgeon General's conclusions with regard to this disease.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty as to whether cigarette smoking causes stroke?

A: Yes, I conclude that smoking causes stroke.

Q: Doctor Samet, did you also investigate whether cigarette smoking causes atherosclerosis and aortic aneurysms?

A: Yes, I did.

Q: Can you describe these diseases to the Court?

A: Yes. We talked before about how atherosclerosis affects the blood vessels in the heart or the blood vessels leading up to the brain. Atherosclerosis refers to the development of plaque lesions, that is, growths in the arteries and the consequences of those growths which can include an inadequate blood supply to parts of the body downstream from the growth, for example, to a leg or an organ. These plaques are also spots where blood clots form. The little pieces of plaque

can also break off and move down and block smaller vessels, arteries downstream from where the plaque is.

Aortic aneurysm refers to a serious problem of widening of the aorta. The aorta is the main tube or artery that takes the blood out of the heart and it travels down the back adjacent to the spine, down through the abdominal cavity, distributing blood to the major organs in the abdomen, and then on to the legs. An aneurysm of the aorta is an abnormal widening of the aorta. At its worst, an aneurysm can widen and then burst. Unless the leakage of blood from the aorta is very slow, so that the bleeding can be stopped, the victim will die. The blood will just simply be pumped out wherever the aneurysm and subsequent rupture has occurred.

Q: What are some of the primary symptoms of atherosclerosis?

A: Some persons with atherosclerosis may have pain that comes and goes, as discussed with angina. That condition is called intermittent claudication. People with this condition typically develop pain in the legs when they exert themselves, because the blood supply cannot keep up with the oxygen needs of the exercising muscles. There may be blood clots that form on the plaques and cut off the flow altogether.

Q: What are the treatments for atherosclerosis?

A: They are quite variable. It would depend on the amount of the atherosclerosis, where it is, and what the consequences are. Medications might be used or surgical treatment might be needed to remove or to bypass the blockage.

Q: What are some of the primary symptoms of aortic aneurysm?

A: The range of symptoms is variable. Some aneurysms are detected while asymptomatic by x-ray or other imaging. One presentation is sudden collapse from rupture. There may be pain as the aorta widens.

Q: What types of treatment are used to treat aortic aneurysms?

A: For aortic aneurysm, ultimately surgery is needed for this condition.

Q: Are there any increased health concerns associated with the treatment of a smoker with an aortic aneurysm?

A: Smokers are at greater risk for complications.

Q: As part of your investigation in this case, did you research the published scientific literature search regarding the relationship between cigarette smoking and atherosclerosis and aortic aneurysms?

A: Yes, I did.

Q: Doctor, when did the Surgeon General of the United States first conclude that smoking is a cause of atherosclerosis and aortic aneurysm?

A: There was a causal conclusion in 1989. Atherosclerosis was first addressed in 1969, and the report stated, "Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries." If the Court looks at U.S. Exhibit 17187 (JS046K), the Court can see a summary of the Surgeon General's conclusions with regard to atherosclerosis and aortic aneurysm.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty as to whether cigarette smoking causes atherosclerosis and aortic aneurysm?

A: Yes, I conclude that smoking causes atherosclerosis and aortic aneurysm.

Q: Doctor Samet, let's turn now to peptic ulcer. What is peptic ulcer?

A: Peptic ulcer refers to the erosions or ulcers that occur usually at the end of the stomach where the stomach empties out into the duodenum, and then in the first part of the duodenum, which is the very first part of the small intestine.

Q: What are the symptoms of peptic ulcer?

A: The symptoms may include pain, particularly pain when the stomach is empty. People may present with bleeding if the ulcer becomes deep enough and erodes into a blood vessel. There may actually be severe bleeding. Among other symptoms, people may have discomfort when eating and may experience weight loss.

Q: What methods are used to diagnose peptic ulcer?

A: Typically, first the diagnosis needs to be made by looking into the stomach with a tube very much like the bronchoscope, except for looking into the esophagus and stomach and duodenum.

Q: What treatments are used on peptic ulcers?

A: The basic treatment is medication, and for those individuals who have bleeding, surgery may be necessary to identify the bleeding point and sew it over so that the bleeding can be stopped.

Q: As part of your investigation in this case, did you investigate the published scientific literature regarding smoking and peptic ulcer?

A: Yes.

Q: Doctor Samet, when did the Surgeon General of the United States first conclude that smoking is a cause of peptic ulcer?

A: There was a causal conclusion in 2004. The causal relationship between smoking and peptic ulcer was first addressed in 1964, and the report stated, "Epidemiological studies indicate an association between cigarette smoking and peptic ulcer which is greater for gastric than for duodenal ulcer." If the Court looks at U.S. Exhibit 17191 (JS046N), the Court can see a summary of the Surgeon General's conclusions with regard to this disease.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Doctor, based on your education, training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking

and health, do you have an opinion regarding whether cigarette smoking is a cause of peptic ulcer?

A: Yes. Smoking is a cause of peptic ulcer.

Q: Doctor Samet, have studies addressed smoking and cataracts?

A: Yes. Over the last decade approximately, a number of studies have addressed risk for cataracts in persons who smoke. A cataract is an opacity of the lens of the eye; they are thought to arise because of oxidation damaging the proteins of the lens. Sunlight, with damage from ultraviolet radiation, is one suspect risk factor for cataract. A number of epidemiological studies have been carried out on cataract and smoking. These have been of either case-control or cohort designs. The 2004 Surgeon General's Report listed 17 such studies. Most of these studies showed an increased risk for smokers compared to never-smokers with relative risks ranging between two and three. A number of studies showed a dose-response relationship with the amount smoked.

Q: Doctor, turning to U.S. Exhibit 17196 (JS046-), did the 2004 Surgeon General's Report reach a conclusion on smoking and cataract?

A: Yes, the 2004 report concluded that smoking was a cause of nuclear cataract. There was also suggestive evidence that smoking cessation reduces the risk for opacification of the lens. The report commented on the biological plausibility of smoking as a cause of cataract, noting that smoking does cause oxidative injury and that the lens lacks the capacity to repair itself.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking and health, do you have an opinion regarding whether cigarette smoking is a cause of cataracts?

A: Yes. It is my opinion that smoking is a cause of cataracts.

Q: Doctor Samet, has cigarette smoking been examined as a risk factor for low bone density?

A: Yes, there has been substantial research on smoking and low bone density as well as on risk for fractures of the long bones, including the humerus (bone of the upper arm), hip, and femur (the long bone of the thigh). Low-bone density is an indication of the presence of osteoporosis.

Q: What have these studies shown?

A: There have been two lines of scientific investigation: studies of bone density in smokers compared with nonsmokers, and studies of smoking as a risk factor for fracture. The evidence shows a clear association between smoking and lower bone density, an indicator of osteoporosis, and smoking in post-menopausal women. The evidence is less clear in pre-menopausal women and in younger men. There is substantial and consistent evidence on smoking and hip fracture, but the evidence is not as consistent for fractures of other bones.

Q: Is it biologically plausible that smoking would contribute to low bone density?

A: Yes, there are a number of mechanisms that have been proposed, including, for women, the anti-estrogenic effects of smoking.

Q: Turning to U.S. Exhibit 17198 entitled, "Conclusions on Diseases Caused by Smoking: Low Bone Density," has the Surgeon General reached a causal conclusion on bone mass and also on risk of fractures?

A: Yes, the Surgeon General offered a number of conclusions on this topic in the 2004 Report and also the topic was addressed in earlier reports. In 2004, the Surgeon General did conclude that the evidence showed a causal relationship between smoking and low bone density in post-menopausal women. A causal conclusion was also made for smoking and hip fracture.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Doctor, based on your education, training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking and health, do you have an opinion regarding whether cigarette smoking is a cause of low bone density in post-menopausal women?

A: Yes. It is my opinion that smoking is a cause of low bone density in post-menopausal women.

Q: Has smoking been assessed as a risk factor for adverse reproductive outcomes?

A: Yes, there is a substantial literature exploring a wide range of effects of smoking on reproduction; these include fertility, fetal development, and pregnancy outcome. There is a complicated and voluminous body of evidence that was reviewed in the 2001 and 2004 Reports of the U.S. Surgeon General.

Q: Could smoking plausibly affect reproduction?

A: Yes, reproduction is complex and there are many aspects of reproduction that are could be adversely affected by smoking given the many toxins in tobacco smoke. Many of these toxins reach the fetus. For example, for the developing fetus, smoking by the mother delivers nicotine and other active compounds to the fetus, and it also reduces oxygen delivery to the fetus. There are a number of mechanisms by which smoking could reduce fertility, including effects on both males and females.

Q: Has the Surgeon General reached conclusions on smoking and reproduction?

A: Yes, within a number of specific areas.

Q: Directing your attention to U.S. Exhibit 17193 entitled, "Conclusions on Diseases Caused by Smoking: Reproductive Outcomes," has the Surgeon General reached a conclusion on fertility and smoking?

A: Yes, in the 2004 Report, the Surgeon General found a causal relationship between smoking and reduced fertility in women, although the evidence was not sufficient to infer a causal relationship of active smoking with reduced sperm quality.

Q: Has the Surgeon General reached conclusions on pregnancy and pregnancy outcomes?

A: Yes, there are a number of adverse effects of smoking on pregnancy and pregnancy outcomes. In the 2004 Report, the Surgeon General offered four causal conclusions: maternal

smoking causes 1) premature rupture of the membranes, placenta previa, and placental abruption; 2) Smoking reduces risk for preeclampsia; 3) maternal smoking causes pre-term delivery and shortened gestation; and 4) maternal smoking causes fetal growth restriction and low birth weight.

Q: Did the Report also explore smoking during pregnancy with regard to risk for congenital malformations and infant mortality, and adverse effects on child development?

A: Yes, these outcomes were explored as well. These are difficult topics for investigators, particularly cognitive development because of the difficulty of tracking development. The evidence was found to be suggestive for possible causation of oral clefts by maternal smoking, but not for other congenital malformations. The evidence was considered sufficient to infer causal association between Sudden Infant Death Syndrome (SIDS) and maternal smoking.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Doctor, based on your education, training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking and health, do you have an opinion regarding whether maternal cigarette smoking is a cause of reduced fertility in women?

A: Yes. It is my opinion that smoking is a cause of reduced fertility in women.

Q: And based on your education, training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking and health, do you have an opinion regarding whether maternal cigarette smoking is a cause of 1) premature rupture of the membranes, placenta previa, and placental abruption; 2) pre-term delivery and shortened gestation; and 3) fetal growth restriction and low birth weight?

A: Yes. It is my opinion that maternal smoking causes 1) premature rupture of the membranes, placenta previa, and placental abruption; 2) pre-term delivery and shortened gestation; and 3) fetal growth restriction and low birth weight.

Q: Doctor, based on your education, training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking and health, do you have an opinion regarding whether maternal cigarette smoking is a cause of SIDS?

A: Yes. It is my opinion that maternal smoking is a cause of SIDS.

Q: Doctor, previously you identified another condition caused by cigarette smoking called diminished health. What is diminished health?

A: By "diminished health," I am referring to the general effect of cigarette smoking on a smoker's health status, the poorer general health status of smokers compared to non-smokers, and the general poorer respiratory health of the smoker, including respiratory symptoms and an increased risk for respiratory infections, pneumonia, influenza, and other respiratory diseases.

Q: How are these problems of diminished health manifested?

A: The diminished health of the smoker is manifested in many ways: a general requirement for more medical services; more absenteeism from work; more respiratory symptoms; and an

increased risk for more severe respiratory infections and even death from pneumonia. Smokers also report having poor health far more often than nonsmokers.

Q: What are some of the treatments for this condition of diminished health?

A: The treatments vary. I have described a general requirement for more medical services. The respiratory conditions might require specific therapy, antibiotic treatment or hospitalization for pneumonia.

Q: What kinds of treatment are used with respect to hospitalization for pneumonia, for example?

A: When people are hospitalized with pneumonia, the treatment varies depending on the severity of the pneumonia. But typically treatment involves antibiotics. If a smoker were admitted to the hospital with pneumonia, the smoker might be sick enough to need oxygen or if very sick, the smoker might even need to be placed on a respirator, a breathing machine to provide some assistance to their breathing until the lung recovers.

Q: Doctor Samet, have you done an investigation of the published scientific literature regarding whether cigarette smoking causes diminished health?

A: Yes, I have, and I was co-author on the chapter on this topic in the 2004 Surgeon General's Report.

Q: Was the topic of diminished health covered in the 2004 Surgeon General's Report?

A: Aspects of the components of diminished health had been reviewed in previous reports, however, the 2004 report comprehensively reviewed the topic, and presented a unifying concept that brought together these elements.

Q: What specific components were reviewed in the 2004 report?

A: The chapter on diminished health standards began by setting out a biological foundation for considering diminished health as a consequence of smoking. The chapter addressed some of the general health consequences of smoking, such as the general oxidative stress experienced by smokers, and the depletion of antioxidant defense mechanisms in smokers.

Q: What specific health outcomes were considered?

A: A wide range was considered, but the chapter focused specifically on absenteeism, medical services utilization, post-operative complications, and health status.

Q: How extensive was the review?

A: Lengthy tables were presented on each of these components. The relative evidence is extremely comprehensive.

Q: Turning to U.S. Exhibit 17197 (JS046-), did the Surgeon General's Report reach a conclusion on diminished health status?

A: Yes, the 2004 Report concluded that the evidence is sufficient to infer a causal relationship between smoking and diminished health status.

Q: Did this chapter reach any other conclusion with regard to diminished health status?

A: The chapter also noted that the evidence is sufficient to infer causal relationship between smoking and increased risk for adverse surgical outcomes.

Q: Did the Surgeon General reach any other conclusions with respect to diminished health status?

A: Yes, in a separate chapter the report addressed pneumonia and influenza, and reached a new conclusion, finding that the evidence is sufficient to infer a causal relationship between

smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease."

Q: On what basis did the Report reach these conclusions?

A: The Report applied the well-known Surgeon General's criteria for causality to the evidence. The report noted the range of outcomes and studies available, and the general consistency of their findings. While the strength of association was variable across the studies, the association of smoking with the various components of diminished health status could not be explained by confounding or other biases.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Doctor, based on your education, training, your expertise in the science of smoking and health, and your review of the published scientific literature on the science of smoking and health, do you have an opinion regarding whether cigarette smoking is a cause of diminished health?

A: Yes. It is my opinion that smoking is a cause of diminished health.

Q: Turn now to U.S. Exhibit 17203 (JS002) entitled, "Diseases and Other Adverse Health Effects Caused by Smoking," can you tell the Court what is depicted on this exhibit?

A: Yes. This exhibit is a summary of the diseases and other adverse health effects that I concluded were caused by cigarette smoking.

Q: What are those conditions and diseases?

A: Lung cancer, COPD, laryngeal cancer, oral cancer, esophageal cancer, stomach cancer, liver cancer, pancreatic cancer, kidney cancer, bladder cancer, cervical cancer, acute myeloid leukemia, cerebral vascular disease or stroke, coronary heart disease, aortic aneurysm, atherosclerosis, peptic ulcer, cataract, low bone density, adverse reproductive outcomes, and diminished health status.

Q: So far you have been talking largely about the effects of active smoking on adults. Regular smoking often begins in adolescence. Are there adverse health effects associated with active smoking among youths?

A: Yes, the health effects of active smoking have been investigated in adolescent and young adult smokers since the 1960s.

Q: What have these studies shown in regard to adverse health effects of active smoking among adolescents and young children?

A: Of course, children are not at risk for the chronic diseases caused in adults after many years of active smoking, such as cancer, COPD, and cardiovascular disease. However, some of the same symptoms and other ill effects that are seen in adults are also found in children who smoke.

Q: What effects have been observed?

A: The most extensive published scientific literature relates to respiratory symptoms and lung function. With regard to respiratory symptoms, those children who smoke have higher frequency of cough, sputum production, wheezing, and shortness of breath. Additionally,

reductions of lung function have been shown when comparison is made between children who smoke and those who do not.

Q: Have these adverse consequences of active smoking in children been reviewed by the Surgeon General and the Surgeon General's Reports?

A: Yes, this topic was included in the 1994 Report which addressed the general topic of prevention of tobacco use among young people.

Q: What conclusions were reached in this report with regard to adverse consequences of smoking by young people?

A: The Surgeon General's Report concluded that cigarette smoking during childhood and adolescence does lead to increased rates of respiratory symptoms, increased number and severity of respiratory illnesses, decreased physical fitness, a slowing of the rate of lung growth and the maximum level of lung function obtained during the phase of lung growth which ends in late teenage years. The Report also commented on an unfavorable lipid profile with regard to cardiovascular risk. That is, adolescents who smoke tended to have blood lipids predicting higher cardiovascular risk than nonsmokers did.

Q: What is the significance of these adverse health effects?

A: Not surprisingly, since active smoking causes lung injury, the lungs of children respond just as do those of adults. Most critically, the lungs of children are growing and smoking impairs the rate of growth. Thus, the maximum level achieved for a child who smokes is diminished. There is less reserve to guard against the consequence of future decline with aging and continued smoking. Of course, the child who smokes is at high risk to continue smoking throughout adulthood.

Q: Doctor, what is the "International Classification of Diseases, 9th Edition?"

A: This is the ninth revision of the system used to place codes for various diseases on medical records, including cause of death and research records. It is often referred to as the ICD-9 code. It is also used for billing purposes.

Q: Have you reviewed the "International Classes of Diseases, 9th Revision, Clinical Modification, 4th Edition?"

A: Yes, I have.

Q: Does that document form a part of the investigation and basis of the opinions that you have expressed in your testimony?

A: Yes.

Q: Do you consider that document to be a reliable authority in the published scientific literature?

A: Yes.

Q: Doctor Samet, please direct your attention to U.S. Exhibit 17162 (JS069) entitled, "International Classification of Diseases, 9th Revision, (ICD-9) used for Health Care Costs Model," can you explain to the Court what is set forth in that exhibit?

A: This exhibit gives the major diseases that we have discussed that are caused by smoking and used in the health care costs model. Opposite each of those diseases are numbers representing ICD-9 codes that correspond to diagnoses of the disease or the direct consequences of the disease. For cerebral vascular disease and coronary heart disease, there are several codes.

Q: Have you had an opportunity to review medical claims information and billing records in the past?

A: I have reviewed some records.

Q: Do they contain ICD-9 codes?

A: Yes, they do.

Q: Have you used ICD-9 codes in your research?

A: Yes, I have.

Q: Are you familiar with their use in coding medical encounters for billing purposes?

A: Yes, I am.

Q: Doctor, let's turn back to U.S. Exhibit 17162 (JS069), you talked about "direct consequences" of the diseases listed on that exhibit that can also result in health care costs?

A: Yes. For example, for cerebrovascular disease or stroke, ICD-9 code 342 is simply the number that has been given to one of the consequences of stroke, which we talked about previously. That condition is weakness of part of the body or hemiplegia or hemiparesis. So the looking at the codes beside cerebrovascular disease or stroke, 430 to 438 refer to stroke itself while 342 refers to a complication of stroke.

Q: Does the medical community have a name for those kinds of direct consequences?

A: Physicians often use the word sequelae. Complication is also a term often used to talk about some of these effects.

Q: Do the ICD-9 codes for these complications appear on U.S. Exhibit 17162 (JS069)?

A: Some do. As I mentioned for stroke, code 342 is the code for hemiplegia. For coronary heart disease, 410 to 414 are the primary codes; other ICD-9 codes include codes for heart failure or failure of the heart muscle to be able to keep up with the needs of the body after a heart attack, and also disturbances of the heart rhythm that might follow a heart attack.

Q: Doctor, are there other direct consequences of diseases that we have discussed thus far that are caused by cigarette smoking that are not listed on U.S. Exhibit 17162 (JS069)?

A: Yes. ICD-9 codes are not listed for the metastasis that might arise from the smoking caused cancer. For example, there is no code listed for involvement of the brain or the bones by cancer or perhaps damage to the spinal cord and paralysis that might come from metastasis to or around the spinal cord. There are many other complications, pneumonia for example, that might come with lung cancer. So I have not attempted to put together these codes in a way to address every possible sequelae or complication of the smoking-caused diseases.

Q: Are prescription drugs assigned ICD-9 codes?

A: No, they're not.

Q: Are any prescription drugs listed on U.S. Exhibit 17162 (JS069)?

A: No.

Q: Have you listed the ICD-9 codes corresponding to diminished health on U.S. Exhibit 17162 (JS069)?

A: No.

Q: Why aren't there codes corresponding to diminished health listed?

A: It would be very difficult to assemble a full list of the codes corresponding to the many ways in which diminished health status could lead to health care encounters.

Q: Why is that?

A: In part because of the somewhat non-specific nature of this diminished health status condition and the specific details of the coding system.

Q: Doctor Samet, as part of your investigation in this case, have you also reviewed published scientific literature regarding the role of socioeconomic status in smoking and disease?

A: Yes, I have.

Q: How many articles have you compiled that deal with that subject?

A: There are about 100 articles where socioeconomic status has been considered as to whether it affects the causal relationship between smoking and disease.

Q: What is socioeconomic status?

A: Socioeconomic status is a technical term used to refer to the sort of relative economic well- being of persons in our society.

Q: What role, if any, does socioeconomic status play in the causal relationship between smoking and disease?

A: Study after study, including the 100 or so that I have mentioned, show that smoking has risks for people at the higher end and the lower end of the socioeconomic scale alike, and certainly the effects of smoking are not due to any failure to control for socioeconomic status in examining the effects of smoking.

Q: Did you have any involvement with respect to the modeling of health care costs, cases of disease and premature deaths in this case?

A: Yes, I did. I worked with Drs. Scott L. Zeger, Timothy Wyant and Leonard S. Miller.

Q: Did you offer advice and observations to Drs. Miller, Wyant and Zeger regarding smoking and the diseases caused by smoking?

A: Yes, I did in this case and I also provided similar advice to them in 1996 through 1998 in connection with their work in a case that was brought by the State of Minnesota against the tobacco industry and in connection with other cases brought by states around that time.

Q: In this case, did you supply them with the ICD-9 code numbers of major diseases caused by smoking?

A: Yes, I did.

Q: Are those ICD-9 codes listed on U.S. Exhibit 17162 (JS069)?

A: Yes.

Q: That is a list that you compiled?

A: That's correct.

Q: Did you have any assistance from Drs. Zeger, Wyant and Miller in compiling that list?

A: No.

Q: Did you advise them as to whether all health care costs that are caused by cigarette smoking were captured by the ICD-9 codes that are listed on U.S. Exhibit 17162 (JS069)?

A: Yes.

Q: What did you tell them?

A: I told them that as we have discussed previously, all the sequelae of the smoking-caused diseases cannot be captured in the ICD-9 codes. And, I advised them that the consequences of diminished health status could not be captured in the ICD-9 codes because, as we discussed earlier, diminished health can be manifested in a variety of ways, including surgical complications, doctors visit for nonspecific or respiratory complaints, and absenteeisms from work. For this reason, diminished health may reasonably be reflected in such measures as self-reports of poor health status.

Q: Did you provide any advice to them regarding screening by age for the purposes of input into their modeling?

A: Yes, I did.

Q: For what purpose?

A: I advised them about screening data to be certain that they were identifying persons as having the disease who really had it; that is, to try to avoid false positive identification of persons as having a smoking-caused disease.

Q: What did you recommend in terms of the screening?

A: With regard to age, I indicated that except with regard to diminished health, there should be age screens put into place to screen in the data.

Q: What did you recommend?

A: I recommended that ICD-9 codes corresponding to certain causes of disease should not be considered as caused by smoking unless the person with that ICD-9 code had reached age 40.

Q: Why did you make that recommendation?

A: Because these diseases are relatively uncommon among persons under 40 years of age. I already talked about temporality and how physicians do not generally see these diseases until people have smoked for a substantial period of years, often 20 or more. I recommended the age screen so as to avoid those instances where there has not yet been enough evidence collected to reach a causal conclusion. That is not to say that a younger smoker could not have developed the disease as a result of smoking, but rather that sufficient evidence has not been gathered at this time.

Q: Doctor Samet, did you also offer advice about the conceptual structure of the model?

A: Yes, I did.

Q: What suggestions did you make with regard to its conceptual structure?

A: I suggested that since we know that smoking causes disease and smoking-caused diseases result in health care utilization and health care costs, that the model should address smoking-

caused diseases. I also suggested two broad classes of disease: those where a very high proportion of the cases are caused by smoking which, as I have explained to the Court, are lung cancer, COPD, and laryngeal cancer; and, I suggested that the other major diseases that are caused by smoking be grouped together separately.

Q: Did you have any other discussions concerning the sequelae or complication that arise from these groups of diseases that are caused by smoking?

A: Much as we have discussed here, we had discussions on a number of occasions over the last eight years with regard to the general nature of these diseases, how they progress and are typically treated, likely precursors—such as respiratory difficulties or chest pains or pneumonia—and likely subsequent complications, such as metastatic cancers, surgical complications, respiratory compromise, paralysis, and so on.

Q: Did you identify any other subpart of the conceptual model?

A: I also identified that health care costs arise from diminished health status, and confirmed that another path to calculating health care costs that are caused by smoking was poor health status.

Q: Did you provide any advice in connection with the calculation of premature deaths?

A: Yes. We discussed authoritative sources for relative risks of death for current and former smokers compared with never smokers. I suggested that it is reasonable to rely on those that were derived from the CPS II study, as reported in the 1989 Surgeon General's Report and Monograph No. 8 from the National Cancer Institute.

Q: Doctor, other than your advice on diseases and screenings that you have discussed, did you offer any advice as to what the plaintiffs' model should measure?

A: No, I did not.

Q: Did you provide any advice to Drs. Zeger, Wyant and Miller regarding statistical methods to be used in the model?

A: No, I did not.

Q: Did you provide to Drs. Zeger, Wyant and Miller any advice regarding modeling methods?

A: No.

Q: Doctor, let's move now to the subject of low machine-measured tar and nicotine products. First of all, what is "tar," and what is FTC tar yield?

A: Tar has a technical definition which is the particulate matter or solid material deposited on a special filter when a cigarette is smoked in a standard smoking machine according to a specified protocol. In non-technical terms, tar might be thought of as the solid material in tobacco smoke.

Q: Have you written about tar yield and the measurement of tar yield?

A: Yes, it was a topic that I contributed to in Monograph 7 of the National Cancer Institute series. I have also addressed tar yield and disease risk in Monograph 13 of this same series, and in the 2004 report of the U.S. Surgeon General, for which I was the Senior Scientific Editor. I also covered this topic in the 2002 monograph of the International Agency for Research on Cancer. I have also done research on the health implications of tar yield and published a number of articles on the topic.

Q: Who sets the protocol for measuring tar yield?

A: The protocol for measuring both tar and nicotine yield is specified by the Federal Trade Commission, but the actual testing is carried out by a central laboratory funded by the cigarette companies themselves, who then report the tar and nicotine yield numbers to the FTC.

Q: Can you tell us how tar yield is measured using the FTC protocol?

A: In short, the cigarettes are smoked in a machine and the smoke is passed through a filter called a Cambridge Filter, and the FTC tar yield refers to the weight of the material deposited on the filter less the weight of any water and nicotine. Cigarettes are sampled from those being made according to a specified sampling scheme and brought to the test laboratory; the machine smokes 20 cigarettes at a time according to a predetermined pattern of smoking, essentially a puff every minute; the puff lasts two seconds, and the volume of the puff is 35 milliliters, a little over two teaspoons equivalent; and the cigarette is then smoked down to a specified length. The smoke is passed through the Cambridge filter, just a filter pad that collects the materials that are in the smoke that are solid or gases that might be absorbed, onto the filter.

Q: How is tar then measured?

A: Tar is the weight on the filter, the gain in weight of the filter after the cigarette is smoked, with subtraction of the weight of water and the weight of nicotine. This is the basis for the FTC tar yields that are printed on packs of cigarettes and in advertising.

Q: How did the FTC protocols come about?

A: They have their origins quite some time ago, in part in an early paper titled "Determination of Particulate Matter and Alkaloids in Cigarette Smoke," published by Dr. C.L. Ogg, who made observations on smoking patterns and how people puffed and how much he thought they puffed. His work, and the work of others, became the basis for the FTC protocol, which I believe has been in place since 1967.

Q: Where is the FTC tar yield of a particular cigarette displayed?

A: The tar yield, as well as the nicotine yield, as determined by the cigarette companies and reported to the FTC, are printed on the cigarette pack itself, as well as advertisements for the cigarettes. It is usually in small text somewhere on the pack or advertisement.

Q: What trend has there been in the last 50 years with respect to tar and nicotine yields of commercially available cigarettes?

A: The tar and nicotine yields of cigarettes smoked in the United States, as measured by a smoking machine according to the FTC protocol, have dropped substantially since the 1950s. This drop has coincided with the introduction of filters, ventilation holes that dilute the smoke with air, and other design/manufacturing changes.

Q: Have researchers studied the relationship between FTC measurements, that is, tar and nicotine yields as reported from the FTC method, and the levels of tar components and nicotine actually entering into the bodies of smokers?

A: Yes. A number of studies have used biomarkers of dose for specific tobacco smoke components, including carboxyhemoglobin (hemoglobin bound to carbon monoxide rather than to oxygen) and cotinine (a metabolite specific to the breakdown of nicotine). Biomarker is just a general term for measurement of some compound in a biological material. We measure these substances, or biomarkers, as quantitative indicators of how much a person has smoked, and of the amount of biological materials reaching his or her lungs, and then getting into his or her bloodstream. Using these methods, researchers have explored the relationship between the FTC-yield measurements and the levels of biomarkers in smokers.

Q: What have these types of studies shown?

A: Generally speaking, research using these biomarkers has indicated little, if any, correlation between the FTC-yield of tar or nicotine, and the levels of the biomarkers measured in smokers. These studies have been conducted both in the population context and in laboratory settings. For example, in one study (Coultas and colleagues 1988) researchers collected saliva for the analysis of cotinine levels, and breath samples for measurement of carbon monoxide levels in a population sample of Hispanic persons from New Mexico who were included in a respiratory health survey. After taking account of the numbers of cigarettes smoked, the levels of biomarkers were not associated with the yields of tar and nicotine of the current brand that was being smoked. Another study (Djordjevic and colleagues 2000) evaluated smoking patterns and biomarkers in the laboratory setting, contrasting smokers of medium-yield and low-yield cigarettes. The smokers had greater puff volumes and puff frequencies than are specified in the FTC protocol and had substantially greater intakes of tar and nicotine than those implied by the brand listings.

Q: What does this mean?

A: These results suggest that there is little difference in the levels of biomarkers comparing smokers of higher yield tar/nicotine cigarettes and lower yield tar/nicotine cigarettes, as measured by the FTC method. This implies that doses of carcinogens or other toxic materials that smokers ingest have little relationship, if any, to the FTC tar yield. This, in turn, suggests that the gradual reduction in tar yield over the past several decades has not resulted in a reduction in smokers' exposure to carcinogens, and that the FTC test method is not informative with respect to lung cancer risk or to the risks of smoking-caused diseases generally.

Q: How do you explain this?

A: There are several explanations for this lack of correlation. First, the smoking pattern of the machine is not representative of how people smoke; in other words, the machine does not smoke like a person, or even the average person. It uses a pattern of puffing that is based on very old information. Second, the ventilation holes in the filter, which are not covered when the end of the cigarette is inserted into the machine, are generally covered by smokers as they hold the cigarette and puff. Third, smokers tend to compensate for the reduced yield of nicotine by increasing the volume of puffs (that is, the volume of smoke they pull into their mouths), the number of puffs per cigarette, and the number of cigarettes smoked. This compensation is not replicated by the test machine. In this manner, smokers can generate similar levels of biomarkers, even though they smoke cigarettes that are advertised as "Low Tar" or "Low Nicotine."

Q: Cigarette manufacturers have been offering lower tar yield products for some time now, correct?

A: Yes, for a number of decades.

Q: Let's define our terms first. What does "Low Tar" mean to you?

A: The FTC measurement set the context for interpretation. "Low tar" means less tar as measured by the FTC protocol, relative to higher tar cigarettes as measured by the same method. This definition must be distinguished from low tar as defined by the amount, or dose, of tar actually ingested by a smoker, that is, a definition based on what happens with people, not machines. These two concepts are very different, and simply defining a cigarette as "Low Tar" under the FTC definition does not mean that the smoker of such a "Low Tar" cigarette will receive a significantly lesser dose as he or she actually smokes the cigarette and inhales the smoke. In fact, evidence with respect to smoker compensation and biomarkers shows that those

smokers who switch to “Low Tar” cigarettes modify their pattern of smoking to obtain the same or similar amounts of tar and nicotine as from the “High Tar” cigarettes they used to smoke. The bottom line is that a “Low Tar” label-based brand under the FTC protocol does not mean that a smoker is actually ingesting “Lower Tar” than from any other cigarette.

Q: What is the title of this next demonstrative exhibit, marked U.S. Ex. 17,173?

A: This is called "Time Trends of Filter Tip and FTC Protocol Measured Tar and Nicotine Yields.”

Q: What are the sources of the information in this exhibit?

A: The 1999 and 2000 Federal Trade Commission Reports, the 1989 Surgeon General’s report, a 1997 paper by Dietrich Hoffmann called “The Changing Cigarette 1950-1995,” and industry documents.

Q: Tell us what this exhibit shows.

A: This exhibit summarizes several groups of data. We can see the percentage of U.S. cigarettes with filter tips starting in early 1950s or so and moving forward in time up to 2000. And you can see the rapid rise across the '50s, '60s, of the use of filter cigarettes, so that today, except for a very small percentage of cigarettes sold in the United States, almost all of the cigarettes smoked are filtered cigarettes.

Q: What do the other two other lines on the exhibit show?

A: The first shows nicotine yield over time and the second shows tar delivery over the same time period, both tar and nicotine being measured by a machine-based protocol. So this exhibit shows the percentage of U.S. cigarettes with filter tips in blue, and you can see the sales-weighted average for nicotine yield of the cigarettes. As a sales-weighted average for the U.S., we then have milligrams of nicotine. The scale runs from about zero all the way to four

milligrams. You can see a decline starting from some of the earliest data, when that average was up at about three milligrams of nicotine, moving down towards about one milligram in 1990.

The second other line shows the same information, except that we are now looking at tar yield, as measured by the FTC or earlier protocols. The scale has changed here for tar yield, because with tar we're now going from zero to 40 milligrams. At the earliest point, tar yields were about 38 milligrams in the average, and now as the line is moved down over time, it's at about 10 to 12 milligrams of tar as the average of the cigarettes sold in the U.S.

So this exhibit brings together information on filter tips, nicotine and tar, and describes how over time, essentially over 40 years, filter-tip smoking has risen, and in terms of the machine-measured tar yields and nicotine yields, these have declined Over that time there have been a number of well-documented changes in design of cigarettes.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty as to the health risks to smokers of low yield, or "Low Tar" products?

A: Yes I do.

Q: Before stating your opinion, what, if anything, is known about the health risks posed by lower tar products?

A: The evidence on the risk of lower tar products has been growing, but this is a difficult topic for researchers. Investigating the consequences of modifications in cigarettes is difficult because cigarettes have been changing continually over time, so that comparisons cannot be made between groups that have smoked the same cigarettes throughout their entire lives. People

who started smoking in the 1950s then moved on to the cigarettes of the 1960s and 1970s, for example, if they continued to smoke.

The available epidemiological evidence comes from three sources: (1) comparisons of changes in mortality rates for lung cancer and other diseases over time in relation to changes in products used by smokers; (2) case-control studies comparing disease risks in smokers of different types of products; and (3) cohort studies that have tracked smokers over substantial periods of time, as with the study of British physicians, or that have been conducted serially, as with the two American Cancer Society Cancer Prevention Studies, known as CPS I and CPS II.

Q: Have you reviewed this evidence?

A: Yes I have, and over the last few years, the topic has been reviewed by the Surgeon General, the Institute of Medicine, the International Agency for Research on Cancer of the World Health Organization, and the National Cancer Institute. I have been directly involved in all of these reviews except that by the Institute of Medicine.

Q: What has this evidence shown?

A: The relevant evidence is not extensive and not fully consistent across the three sources. Some case-control and cohort studies have shown small reductions in risk, particularly for lung cancer, comparing smokers of filter cigarettes with smokers of non-filter cigarettes. In general, tar yield is only a weak predictor of lung cancer risk after taking account of other aspects of the smoking history. Some have interpreted the rapid decline in lung cancer mortality in younger males in the United Kingdom during the last decades of the 20th century as indicating a benefit of the changing cigarette. However, data from other cohort studies, the British Physicians' study, and CPS I and II indicate rising relative risks of lung cancer over time in smokers

generally. If the changes in cigarette yields had any benefit we would expect these relative risks to be dropping. Instead, they are not.

A recent review by the Institute of Medicine concludes there is little evidence for an important benefit of lung cancer risk from smoking reduced yield cigarettes. The conclusion by the International Agency for Research on Cancer of the World Health Organization (WHO) in 2002 was very similar. This means that for smokers who switch to low tar cigarettes – by the FTC definition – there is no meaningful benefit in terms of reducing their risk of lung cancer. There is no health benefit associated with changing the type of cigarette that you smoke. This is my opinion as well.

Second, with respect to heart disease and COPD, the evidence has also consistently shown that smokers who use low tar products obtain no benefit at all in terms of reducing their risk of acquiring these two diseases. This is also my opinion.

Q: Are these your conclusions alone?

A: No, as I mentioned, several expert reviews carried out by major health agencies over the past several years have reached the same conclusion, including IARC and IOM. Most recently, the 2004 Surgeon General's Report concluded that, "Smoking cigarettes with lower machine-measured yields of tar and nicotine provides no clear benefit to health." This topic was also the focus of an entire monograph of the National Cancer Institute, Monograph 13, which reached a similar conclusion.

Q: Have you reviewed these studies as part of your investigation in this matter?

A: Yes I have.

Q: Do these studies form a part of the basis of your opinions in this case?

A: Yes they do.

Q: Do you consider the studies reliable authorities in the published scientific literature?

A: Yes I do.

Q: Let's discuss the 2004 Surgeon General's Report first. What was your role in the preparation of the 2004 report?

A: As I have mentioned previously, I was the Senior Scientific Editor for the report.

Q: Did the 2004 report draw any conclusion with respect to low yield products?

A: Yes, it did.

Q: What was that conclusion?

A: The four Major Conclusions of the report are listed at the close of Chapter 1, on page 25, of the report. The third Major Conclusion is that, "Smoking cigarettes with lower machine-measured yields of tar and nicotine provides no clear benefit to health."

Q: Can you describe how you and the other authors of the report reached that conclusion?

A: Yes**.** The report looked at this issue in-depth, considering the full range of evidence. First, although machine-measured yields of tar and nicotine have decreased substantially over the past 50 years, the risk of lung cancer in smokers has not declined. More and more smokers are smoking low yield products, as compared to their counterparts in the 1930s, 1940s, and 1950s, yet the risk of these smokers developing and dying from lung cancer is not falling and some studies show that it is rising. If there were a health benefit with respect to lung cancer that paralleled tar yield, we would expect to see some decline in the risk of lung cancer in smokers.

Q: What else did the authors of the report consider?

A: We also assessed more recent data and conclusions from a number of published studies, and these studies suggested no clear health benefit. Two particularly important studies were

those of one million Americans, each carried out by the American Cancer Society, one from 1959-1972, and the second, started in 1980, is ongoing. These studies, and some others, provide insights into whether risks of smoking are changing over time. If there were substantial benefits of the change in tar yield over the 20 years between the two studies, we would expect lower relative risks; instead they increased.

Third, we noted the increase and shift, starting in the 1970s in the prevalence of adenocarcinoma of the lung. In smokers, lung cancer in the early decades of the rise in the disease largely took the form of squamous call carcinoma and small cell carcinoma. Now adenocarcinoma is the most common histological type of the disease. This is a significant development that may be indicative of a change in the delivery of carcinogens by cigarettes over time and a possible detrimental consequence of the use of low yield products. This information is discussed and explained in pages 49 to 61 in the 2004 Report.

We looked at these and other lines of evidence, and came to the conclusion that I stated above. You also see on page 61 under the heading "Implications" that, "The evidence shows that changes in the design of cigarettes intended to reduce tar and nicotine yields have had no significant beneficial consequences for lung cancer risks in smokers."

Q: Let's look at that first point. What are the most telling epidemiological evidence and studies that address the effect of smoking lower yield cigarettes?

A: The first is a comparison of data from the Cancer Prevention Studies, the studies of one million Americans, by the American Cancer Society, studies known as CPS I and CPS II. The clearest finding you can draw from these studies is that regardless of how the cigarettes changed, for smokers in CPS I (1959-1972) versus those in CPS II (1980-1986), relative risks of lung cancer went up. In fact, in more detailed analyses of the data that have been published, the

mortality rates from lung cancer tend to be higher within categories defined by the numbers of cigarettes smoked and the number of years of smoking, comparing the second study with the first. This suggests an increase in the risk of smoking, comparing products for the two groups of smokers.

There is also the British doctors' study, which looked at risks of disease in the first 20 years of the study and the second 20 years of the study. The comparison shows that the relative risk values have gone up comparing the first 20 years (1951-1971) to the second 20 years (1972-1991). Even looking back at older studies that found small reductions in relative risks, even these studies could not mask the fact that during this entire time, over a period of decades, relative risks have been going up and up. Over this time more and more smokers were smoking cigarettes with lower FTC tar and nicotine yields and the sales-weighted tar and nicotine yields declined progressively.

Q: What does this mean?

A: Some earlier studies suggested a small benefit to the use of low tar cigarettes, a modest reduction, perhaps 20% by some research, in the relative risk of lung cancer. The comparison at the time was largely between smokers of non-filtered and filtered cigarettes. Even if we accept that finding, and I do not, we see that this benefit is overshadowed and overwhelmed by the high overall relative risk of lung cancer among smokers over time.

Q: What is Cancer Prevention Study I, or CPS I?

A: CPS I was a study carried out by the American Cancer Society from 1959 to 1972, when tar values of cigarettes were still very high relative to cigarettes available in the 1980s, 1990s and today. Certainly those who developed lung cancer in the 1960s were those who had been smoking the very high tar, mostly unfiltered, cigarettes in the 1950s and before. CPS I was a

very large study that followed over one million people forward in time for 12 years. It looked at death rates from lung cancer in female smokers, male smokers, and non-smokers of both sexes, including former and never smokers. The study also tracked deaths from other causes.

Q: And what is CPS II?

A: CPS II is a much more recent study, also of one million people that began in 1980. One analysis looked at mortality from 1982 to 1988. At this point in time a 60 percent reduction had been achieved, looking at the sales-weighted averages, in machine-measured tar yields in the U.S. market.

Q: Have you reviewed these studies as part of your investigation in this matter?

A: Yes.

Q: Does these studies form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider the studies reliable authorities in the published scientific literature?

A: Yes.

Q: Looking at CPS I and II, was there any change in the death rates for lung cancer among never smokers?

A: No, and this is important for comparing the findings of the two studies. The death rates did not change in never smokers. This means that the higher relative risks represent an increase in the risk of smokers, not a drop in the never smokers.

Q: Turning to the study of British physicians, which is marked as U.S. Exhibit 64,058, why is the comparison of the first 20 years to the second 20 years relevant?

A: In this particular study, Doll and colleagues compared the risks of death from lung cancer and other causes during the first and second 20-year periods of the 40-year follow-up of the

British physician cohort. Lung cancer mortality increased among smokers in the second 20-year period (i.e., 1971 to 1991), even though the products smoked during that time period would have had substantially lower tar and nicotine yield than those smoked during the first 20-year period (i.e., 1951 to 1971). For the first 20 years, the annual lung cancer mortality rate among current smokers was 264 per 100,000, and for the second 20 years, it was 314 per 100,000. Because the never-smoker rate was unchanged at 17 per 100,000 in both periods, the relative risk increased from 15.5 to 18.5.

So this study is relevant because smokers during the second 20 years presumably had smoked more lower tar, filtered cigarettes as opposed to the older filterless higher tar cigarettes. But in the second 20 years, relative risks were higher. In other words, the findings of CPS I, CPS II, and the British doctors study show an increased risk for lung cancer in smokers over time despite the widespread introduction of filter-tipped, low tar cigarettes. The cigarettes were found to attenuate the risk of lung cancer in several earlier epidemiological studies; however, these studies made a comparison at only one point in time. The CPS I / CPS II comparison analyses and the British doctors study look at the impact over broad periods of time.

Q: Have you reviewed that study as part of your investigation in this matter?

A: Yes.

Q: Does that study form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider the article a reliable authority in the published scientific literature?

A: Yes.

Q: What does this evidence tell you?

A: This tells me that any purported benefits of low FTC tar yield cigarettes suggested by some studies, particularly those comparing filter cigarettes with non-filtered cigarettes, have not had any long-range consequences for lung cancer risk in the population. Certainly if lung cancer risk is proportional to tar yield, we would anticipate some drop over the years that machine-measured tar yields were dropping so steeply.

The early epidemiological studies suggested there would be a reduction in the lung cancer death rates, perhaps by as much as 20%, occurring within years of switching from a high-yield to a low-yield cigarette. A 20% reduction in lung cancer deaths would have been a meaningful public health gain. Lung cancer rates were tracked and a reduction never happened to any significant degree. In fact, death rates kept climbing across the last decades of the twentieth century until the recent downturn in men.

The more recent CPS I and CPS II data are consistent with the evidence of the rising death rates, rates that have only very very recently begun to level off, and that is in men and corresponds to cessation of smoking among men.

Q: Doctor, you spoke about a possible health detriment posed by the use of low yield products. The 2004 Surgeon General's Report also noted the rise in adenocarcinoma. Can you explain your comments more fully?

A: Yes. One remarkable change in the epidemiological characteristics of lung cancer over the last 40 years approximately has been a shift in the predominant type of lung cancer. At the beginning of the epidemic of tobacco-caused lung cancer, the leading histologic type was squamous cell carcinoma, which characteristically involves the larger and more central airways of the lung. Since the late 1960s, there has been a shift so that adenocarcinoma is now the most common in both men and women. Interestingly, adenocarcinomas tend to occur more

peripherally in the lung, arising from the smaller airways. One hypothesis is that changes in the cigarette have lead to deeper inhalation with a pattern of deposition of carcinogens in the lung that differed from that typically occurring with the older, higher-yield products. Some have also suggested that the carcinogens in tobacco smoke may have changed, perhaps with greater concentrations of tobacco-specific nitrosamines, which cause adenocarcinoma in exposed animals.

Q: You have given a clear conclusion as to where the evidence stands now. What about in the past?

A: As the evidence on machine-measured yields and health risks accumulated in the 1960s and 1970s, some early studies noted a modest decrease in lung cancer risk and cardiovascular risk for smokers of lower-yield cigarettes, others were inconclusive, and others found no appreciable difference in relative risk at all.

Q: Let's talk about some of those earlier studies in detail. First, what was the 1981 Surgeon General's report?

A: The 1981 Report focused in large part on the changes in cigarettes over the preceding 40 years or so, a period of time where cigarettes changed from being made of chopped tobacco rolled in a piece of paper to a cigarettes with filters using highly processed and even reconstituted tobacco. Now, during this time the machine-measured tar and nicotine values declined by about 60 percent, as I have previously discussed. And the consumption and market share of "lower tar" yield cigarettes increased sharply. In 1981 the Surgeon General looked at the question of whether cigarettes with less tar delivery were actually resulting in a reduction in the risk of known smoking-related diseases.

Q: Do you have an opinion as to why the consumption and market share of low tar cigarettes increased dramatically over the period of time that was the subject of the 1981 Surgeon General's Report?

A: Yes I do. First, there was substantial marketing of these products. Second, some in the public health community during this time were suggesting that tar was what was causing cancer. For those persons who were unable to stop smoking, some health professionals proposed that lower tar products would reduce the risk of cancer. The thinking was that smokers should quit, but if you can't quit, low tar and low nicotine cigarettes might offer some reduction in risk. So large numbers of smokers who heard this message switched to lower tar brands, presumably thinking they were reducing their risk of disease.

Q: Some might argue that what you just described was a recommendation to keep smoking. Is this accurate?

A: Not at all. The 1981 report said that any benefit in smoking cigarettes with lower yields of tar and nicotine would be minimal in comparison with quitting, and that the single most effective way to reduce the risks of smoking was quitting entirely. And this statement, from a technical standpoint, remains true even today.

Q: What did the 1981 Surgeon General's Report conclude with respect to the health benefit of switching to a low tar yield product?

A: The report reviewed a number of lines of evidence on various diseases caused by smoking. One of the conclusions reached was that there was some reduction in the risk of lung cancer for those people smoking filtered cigarettes compared to non-filtered cigarettes. Some studies, and importantly CPSI, found an apparently 20% lower risk of lung cancer among higher yield cigarette smokers as compared to smokers who smoked lower-yield cigarettes. Similar and

even larger reductions were found in some studies, comparing filter to non-filter smokers. But this data must be qualified with other studies and data that have been assembled since that time, studies that have subsequently called this conclusion into question. And, of course, the comparison of filtered to unfiltered cigarettes is not relevant today.

Q: Dr. Samet, I want to direct your attention to the 1981 Surgeon General's Report itself, marked as U.S. Ex. 74,603. What was the title of the 1981 Surgeon General's report?

A: The title and subject were "The Changing Cigarette."

Q: Have you reviewed that Report as part of your investigation in this matter?

A: Yes.

Q: Does that Report form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider the Report a reliable authority in the published scientific literature?

A: Yes.

Q: Directing your attention to paragraph one of the section called "Cancer," can you read the findings of the report?

A: It states on page 101: "Today's filter-tipped, lower 'tar' and nicotine cigarettes produce lower rates of lung cancer than do their higher 'tar' and nicotine predecessors. Nonetheless, smokers of lower 'tar' and nicotine cigarettes have much higher lung cancer incidence and mortality than do non-smokers."

Q: Do you concur with that conclusion?

A: I do not agree with the first part of that conclusion, based on the data available up to now and perhaps a more sophisticated contemporary understanding of the issues. Recent studies of

data from the second Cancer Prevention Study, or CPS II, show that lower tar cigarettes do not produce lower rates of lung cancer than their higher nicotine counterparts. Moreover, the rates of lung cancer being produced by today's cigarettes are essentially unknowable, without careful tracking into the future. We will not know the risk of lung cancer for today's smokers, without watching them for 10, 20, 30 or more years from now. But again, the CPS II evidence suggests generally that there is no reduction in lung cancer rates associated with smoking lower tar products. I do agree with the second statement; smokers of lower tar cigarettes, and this is as true now as it was in 1981, have a much higher risk of lung cancer and higher mortality than non-smokers.

Q: Please turn the page to page 19, the section marked "Cardiovascular Disease," and read the first paragraph for the Court.

A: The report states: "Epidemiological studies show that the incidence of coronary heart disease (CHD) increases as the daily number of cigarettes smoked increases and that the incidence of CHD decreases among those who quit smoking. These dose-related effects suggest that lower 'tar' and nicotine cigarettes might be associated with lower risks of CHD. However, the overall changes in the composition of cigarettes that have occurred during the last 10 to 15 years have not produced a clearly demonstrated effect on cardiovascular disease, and some studies suggest that a decreased risk of CHD may not have occurred."

Q: Do you agree with the conclusion in the last sentence?

A: Yes I do. This conclusion from 1981 is consistent with subsequent lines of evidence on the subject.

Q: Could you turn the page to page 20, to the section titled "Chronic Obstructive Lung Disease" and the read the report's conclusions on this topic at paragraph one.

A: Yes. The report states: "The relationship between cigarette smoking and chronic obstructive lung disease (COLD) is well documented. The constituents of cigarette smoke that are responsible are currently not known. Whether a difference in risk of COLD has occurred with lower 'tar' and nicotine cigarettes as compared with higher 'tar' and nicotine cigarettes is currently unknown."

Q: What is Chronic Obstructive Lung Disease, or COLD?

A: COLD was the terminology at the time in 1981 for what we now call chronic obstructive pulmonary disease, or COPD. As I described previously, it includes emphysema and chronic bronchitis.

Q: Do you concur with the conclusion of the1981 Surgeon General Report with respect to COPD?

A: Yes, this was a correct conclusion for the time. The evidence since that time shows no association of risk for COPD with tar yield and we now have greater insights into the components of tobacco smoke most relevant to COPD.

Q: Doctor, let's go back to the 1981 Surgeon General's report where a benefit was found with respect to the use of "low tar" yield cigarettes, namely a reduction in risk of lung cancer. Based on your education, your training, your expertise in the science of smoking and health, and your review of the scientific literature on smoking and health, do you have an opinion as to why the Surgeon General reached a conclusion somewhat different from the current view?

A: Yes I do. Of course, scientific information was less comprehensive at the time. The Surgeon General's Report did not fully take into consideration the phenomenon of compensation, and how smokers smoke to get a certain amount of nicotine, and will even adjust

their smoking behavior to get the amount of nicotine they seek or are accustomed to. As I stated before, we now know that smokers do this through adjusting their pattern of smoking to smoke more cigarettes, inhale deeper, and take more puffs. In my opinion, we didn't know in 1981 the extent to which smokers would compensate after switching to a "low tar" and low nicotine yield product.

Later studies looking at cotinine showed that smokers of low tar products managed to ingest the same amount of nicotine from smoking cigarettes with yields of less than half of their former high tar, "full flavor" as the industry likes to call them, brands. So when you look at smokers smoking in the real world, as opposed to findings with the FTC machine, you see that there isn't a significant difference in the amount of nicotine smokers are ingesting, regardless of the machine yield. Also, the interpretation of the epidemiological data did not fully account for the complexities in interpreting the case-control and cohort data.

Q: Now, the fact that smokers of low tar/low nicotine yield cigarettes compensate to obtain more nicotine was known back in 1981, correct?

A: By 1981, the phenomenon of compensation had been described in the peer-reviewed medical literature. In fact, the 1981 Report of the U.S. Surgeon General used the term "compensatory smoking."

Q: So didn't the Surgeon General take compensation into consideration when he concluded that there was a modest health benefit for smokers who switched to low tar/low nicotine products?

A: The 1981 report did describe the phenomenon of compensation. Thus, there are two components of this phenomenon: 1) smoking each cigarette so as to obtain the desired intake of nicotine; this occurs by deeper inhalation and perhaps by taking more puffs; and 2) increasing

the number of cigarettes smoked. However, the report did not comment extensively on the implications of compensation for doses of carcinogens and other injurious substances in tobacco smoke. At the time, studies of biomarkers were not so sensitive as now, and some of the currently used measures of exposure to carcinogens, such as adduct levels, were not used widely in research.

Q: Why is this important?

A: It is important because we know that the tar in smoke is very closely linked to nicotine. The more nicotine a smoker ingests, the more tar he or she ingests. If smoking a "low tar" yield cigarette does not result in a change in the amount of nicotine obtained by the smoker, then intake of other components is also not reduced. Thus, the actual intakes of tar and nicotine during product use do not reflect measurements made by the machines and included on the pack or in the advertisements.

Q: But weren't "low tar" cigarettes recommended by some in the public health community for smokers who were unable to quit?

A: Yes, by some. But that recommendation was based on the belief that using "low tar" cigarettes would result in less tar being inhaled by smokers. This did not take place, or certainly not proportionately to the machine yield data.

Q: How does compensation affect the relative risk of cancer?

A: The relative risk of cancer likely depends primarily on the doses of carcinogens reaching target organs. First, inhaling more deeply, taking more puffs, and smoking larger numbers of cigarettes following the switch from a higher-yield to a lower-yield product would likely maintain doses of nicotine and the corresponding doses of carcinogens, following the switch.

Second, epidemiologists have not fully considered the consequences of compensation and its implications for the analysis and interpretation with study data.

Q: What are the issues included in the epidemiological analyses?

A: There are several. First, epidemiologists do not have good measures of some aspects of compensation, such as depth of inhalation. Asking questions about the level of inhaling has proved to be insensitive.

Second, in their analyses, epidemiologists generally control for the number of cigarettes. In essence, this type of analysis assumes that smokers smoke the same number of cigarettes, regardless of nicotine and tar level. Since smokers of lower tar-yield products tend to smoke more cigarettes per day than smokers of higher-yield cigarettes, this analysis approach would tend to reduce the estimated risk of smoking for smokers of lower yield cigarettes. This was the conclusion reached by Monograph 13.

Q: Are there any differences in groups, that is low-yield smokers versus high-yield smokers, that could be masked by epidemiological studies attempting to compare risk?

A: Yes. Epidemiological studies often assume that smokers who switch to low-yield products are similar to smokers who do not. There is evidence that this may not be true. For example, switchers may smoke their cigarettes differently, they may have started smoking later as teenagers, they may attempt to quit more often. Switchers may have smoked less intensely before they switched, when compared to their high-yield, non-switching counterparts. Switchers may have smoked less at younger ages. When these aspects of smoking behavior are not accounted for, study results may be misleading. In addition, switchers are generally healthier group in terms of diet, exercise, and lifestyle in comparison to smokers who do not switch to a low yield product. The cumulative effect of these group differences is that any reduction in the

risks among switchers may be the result of these differences, rather than the fact that they switched to a low-yield product. This was also an observation in Monograph 13.

Q: Can epidemiological studies control for these differences in groups?

A: Yes, but only to the extent that information is available in a study.

Q: Doctor, let's move to Monograph 13, marked as U.S. Ex. 58,700. Can you identify Monograph 13 for us?

A: Yes, I can. Monograph 13 is a book published by the National Cancer Institute in October 2001. It is titled "Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine."

Q: Doctor, did you review Monograph 13 as part of your investigation in this case?

A: Yes, I did.

Q: And does it form part of the basis of your opinions in this case?

A: Yes.

Q: And do you consider it to be a reliable authority in the published scientific literature?

A: Yes, I do.

Q: Did you make any contributions to Monograph 13?

A: Yes, I was one of the authors of Monograph 13 as indicated on page vii. I contributed specifically to the chapter concerned with health risks.

Q: What does Monograph 13 conclude with respect to any health benefit to smokers who switch to low tar/low nicotine yield cigarettes?

A: After a very thorough review of a number of lines of evidence, much of which had been generated after the 1981 Surgeon General's report, the authors concluded that "Overall, they do

not provide evidence that public health has benefited from changes in cigarette design and manufacture over the last 50 years." As I said before, the changes in cigarette design and manufacture refers to the addition of filters and other changes that greatly reduced the machine-measured yields of your average cigarette being smoked.

Q: What recommendations did the authors make with respect to whether smokers of high yield cigarettes should or should not switch to lower yield brands?

A: The authors concluded that, "Existing disease risk data do not support making a recommendation that smokers switch cigarette brands." This is because the "widespread adoption of lower yield cigarettes by smokers in the United States has not prevented the sustained increase in lung cancer among older smokers." A key overall conclusion is that "There is no convincing evidence that changes in cigarette design between 1950 and the mid 1980s have resulted in an important decrease in the disease burden caused by cigarette use either for smokers as a group or for the whole population."

Q: Dr. Samet, do you agree with these conclusions and recommendations?

A: Yes I do. The evidence is clear. We have tracked the risk of lung cancer closely and not seen a fall in relative risks to smokers.

Q: You mentioned earlier a report by the Institute of Medicine, or IOM. Tell us about that report, which is marked U.S. Ex. 32,485.

A: The 2001 IOM report is titled "Clearing the Smoke." This report focused on the scientific basis for reducing the harm caused by cigarettes, and on what the report termed "PREPs," or Potential Reduced Exposure Products. With respect to low yield products, the report assessed at pages 12-20 through 12-23 whether switching to low tar and nicotine cigarettes has shown any health benefit, specifically observing that "while some studies suggest a lower

risk of lung cancer with lower-tar cigarettes, many do not, especially when risk is considered along with biomarkers in relation to smoking behavior." And for the studies suggesting a lesser risk, "there are outstanding questions about smoking behavior that might affect the interpretation of epidemiological studies." So similar to the conclusion of the authors in Monograph 13, there may be unaccounted, unassessed differences in groups, switchers vs. non-switchers, filtered cigarette smokers vs. non-filtered cigarette smokers. So even if some studies show a small reduction in relative risk, we cannot determine if that reduction is the result of lower yield products or unaccounted for aspects of smoking in the study.

Q: Do you agree with these conclusions?

A: Yes I do.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty as to what health benefit, if any, is offered by "Low Tar" cigarettes?

A: The weight of the evidence is that the FTC tar yield of a cigarette is a poor predictor of the risk of lung cancer, COPD, and heart disease to smokers of "low tar" yield products. Even in 1981 there was no documented benefit with respect to reducing risk for COPD and coronary heart disease. And while some earlier studies suggested a modest benefit in terms of lung cancer risk, later, more recent evidence suggests otherwise, namely that there is no benefit. Even excluding the more recent studies and considering only the earlier evidence of a possible benefit for lung cancer risk, those findings must be taken in the context of the overall relative risk of lung cancer comparing smokers to never smokers. This overall risk is so high that even a small reduction is of no public health or medical significance.

Q: Doctor Samet, you briefly addressed the adverse health effects of passive smoking in your earlier testimony. What is passive smoking?

A: Nonsmokers inhale secondhand smoke, the combination of the sidestream smoke that is released from the cigarette's burning end and the mainstream smoke exhaled by the active smoker. The inhalation of secondhand smoke is generally referred to as passive smoking or involuntary smoking. The exposures of involuntary and active smoking differ quantitatively as the active smoker inhales undiluted mainstream smoke, and the passive smoker inhales secondhand smoke, which is diluted sidestream and exhaled mainstream smoke. There are some differences qualitatively in the smoke inhaled by active and passive smokers, but the source is the same: the burning cigarette.

Q: Are there other terms that are commonly used to describe secondhand smoke?

A: Yes, secondhand smoke is sometimes referred to "environmental tobacco smoke," or "ETS."

Q: Doctor, you stated that secondhand smoke consists of both sidestream and mainstream smoke, are there differences between these two?

A: Yes. Sidestream smoke has higher concentrations of some toxic and carcinogenic substances than mainstream smoke due to the lower temperature of the burning core of a smoldering cigarette compared with the higher temperature during the active puffing. Thus, sidestream smoke yields higher concentrations of ammonia, volatile amines, volatile nitrosamines, nicotine decomposition products, and aromatic amines, compared with undiluted mainstream smoke. However, dilution by room air reduces the smoke component concentrations inhaled by the involuntary smoker.

Q: Although nonsmokers inhale both sidestream and exhaled mainstream smoke, do they generally inhale one form more than the other?

A: Yes. Most of the smoke inhaled by passive smokers is contributed by sidestream smoke, as the smoker takes only 10-12 puffs over the approximately 10 minutes that a cigarette is burning.

Q: What are the components of secondhand smoke?

A: Overall the composition of secondhand smoke is that reported for cigarette smoke generally as found in U.S. Exhibit 17108. Thus, secondhand smoke can be presumed to contain over 4,000 compounds, over 50 carcinogens, and many known irritants, toxicants, and mutagens. Some of the known irritants and toxicants include ammonia, formaldehyde, carbon monoxide, nicotine, toluene, nitrogen dioxide, hydrogene cyanide, acrolein, and acetaldehyde. The known carcinogens include, among others, benzo[a]pyrene, 2-napthylamine, 4-aminobiphenyl, benzene, vinyl chloride, arsenic, chromium, and polonium. Many of these specific components are regulated by various air quality standards; for example, with regard to carbon monoxide, which is found in secondhand smoke, the Environmental Protection Agency has set a National Ambient Air Quality Standard that is enforced throughout the country.

Q: How is exposure to secondhand smoke measured?

A: Epidemiologists estimate exposure to secondhand smoke in three ways. First, concentrations of tobacco particles and gases are measured in indoor environments. Tobacco smoke particles are nonspecific markers of secondhand smoke contamination because indoor air contains particles from other sources. Nonetheless, smoking makes a substantial contribution to particle concentrations in many indoor places, and its contribution is readily detected. Small particles are frequently measured because both sidestream and mainstream smoke contain high

concentrations of particles of respirable size range, that is, those small enough to reach the lower respiratory tract. These concentration data are combined with information on time spent in places where concentrations have been measured when we estimate exposure.

Second, tobacco-specific biomarkers are measured in people to ascertain the level of exposure to secondhand smoke and to give an indication of the amounts of toxins entering the body. Nicotine, primarily a vapor or gas in secondhand smoke, is a highly specific marker and it has been widely used to identify and characterize exposure to secondhand smoke. Nicotine and cotinine, its major metabolite, are markers that can be measured in the saliva, urine, and blood of non-smokers. The Centers for Disease Control have been tracking the levels of cotinine in the blood of participants in the National Health and Nutrition Examination Surveys. These are national surveys carried out every ten years. Cotinine is a useful indicator of exposure over a period of several days. Other such markers include thiocyanate, carbon monoxide, and carboxyhemoglobin, and those representing DNA damage such as protein and DNA adducts. It is also possible to measure the concentration of NNAL, a tobacco-specific carcinogen, in the urine.

Third, researchers use a number of indirect methods to measure exposure to secondhand smoke, such as surveys and questionnaires. Epidemiologic studies assess exposure primarily by responses to questionnaires concerning the smoking of household members or fellow employees.

Q: Is any one of these three tools better at measuring secondhand smoke exposure than the others?

A: They are complementary tools and which is "best" to use depends on content and purpose. To date, particularly for epidemiologic research involving large numbers of people, questionnaires remain the best and most feasible method for characterizing usual exposure to

secondhand smoke. However, biomarkers and personal monitoring offer complementary approaches for assessing exposure to tobacco smoke, whether for exposure assessment purposes and public health monitoring, or in the context of an epidemiologic study.

Q: Doctor Samet, you stated that epidemiologic studies often address risks of smoking by household members or coworkers; in what locations have epidemiologists measured these exposures to secondhand smoke?

A: Epidemiologic studies have measured exposure to and the health effects of secondhand smoke exposure in a variety of locations, including homes, workplaces, and public places. Much of the research has focused on exposure in the home, as this type of exposure is often consistent and can be characterized by questioning household members. Some studies have addressed and documented exposures in public settings, such as exposure of nonsmokers in offices and restaurants, as well as in mass transit, such as buses and airplanes. Researchers have also placed monitors on people so that total daily exposures -- those received in the full range of everyday living -- can be measured.

Q: Regarding these studies, how long have scientists been researching the adverse health effects of secondhand smoke?

A: This issue has been studied by researchers and public health organizations for over three decades.

Q: In these studies, Doctor, what adverse health effects were addressed by the researchers?

A: Because research on the adverse effects of passive smoking has been carried out for such a long period of time, a wide range of health effects has been covered. The full life course, beginning with secondhand smoke exposure to the developing fetus *in utero* and extending from

childhood through adulthood, has been researched. The adverse effects include lung cancer and heart disease in adults and many adverse health effects, particularly respiratory, in children. These studies have been conducted both in relation to smoking by the mother during pregnancy, certainly a form of passive smoking by the fetus, and also in relation to exposure of the mother to secondhand smoke during pregnancy.

Q: Have researchers focused on particular adverse health effects with regard to secondhand smoke exposure to a developing fetus?

A: Yes, for studies of the fetus, the emphasis has been on birth weight and also on neurocognitive development.

Q: What adverse health effects from secondhand smoke exposure have researchers emphasized with regard to infants and children?

A: Respiratory health consequences have been the focus of much of the research on infants and children, although childhood cancer risk has also been considered.

Q: What adverse health effects from secondhand smoke exposure have researchers studied for adults?

A: In adults, the primary health outcomes are lung cancer and coronary heart disease; risk for stroke has also been considered.

Q: Doctor Samet, what is meta-analysis?

A: Meta-analysis is an approach for combining data from different studies. In other words, it is a way of averaging results from different studies. It is widely used for summarizing medical evidence.

Q: In your opinion, is meta-analysis a useful tool when analyzing the adverse health effects of passive smoking?

A: Yes. Meta-analysis has been used for summarizing the different studies of secondhand smoke. Fortunately, the effects of secondhand smoke on health are not as strong as for active smoking. To gain the most accurate estimates of the effects, we pool the data from individual studies.

Q: What were the first studies that found an association between passive smoking and lung cancer in nonsmoking adults?

A: Evidence showing that secondhand smoke might cause lung cancer was first brought to our attention by findings of epidemiological studies in 1981. During that year, reports were published from Japan and Greece that indicated substantially increased lung cancer risk in nonsmoking women married to cigarette smokers.

Q: Turning your attention to U.S. Exhibit 22963 , can you identify that exhibit?

A: Yes. U.S. Exhibit 22963 is the paper that Hirayama published in 1981, entitled "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung-Cancer: A Study From Japan," 282 *British Medical Journal*, 183-85 (1981) based on a cohort study in Japan.

Q: Doctor, looking at U.S. Exhibit 17172 entitled, "Hirayama Japanese Cohort Study, Secondhand Smoke and Lung Cancer: Women," would you please describe the Hirayama study to the Court?

A: This exhibit summarizes the results of Hirayama's 1981 report that was based on a prospective cohort study of 91,540 nonsmoking Japanese women. Standardized mortality ratios (SMRs) for lung cancer increased significantly with the amount smoked by the husbands. The SMR takes into account any age differences between populations. The results showed a rising risk for lung cancer from 1.75 for nonsmoking women with husbands who were former smokers or who smoked less than a pack a day to 2.2 for nonsmoking women whose husbands smoked a

pack a day or more. These findings could not be explained by confounding factors and were unchanged when follow-up of the study group was extended. Based on the same cohort, Hirayama also reported significantly increased lung cancer risk for non-smoking men married to wives smoking one to 19 cigarettes and 20 or more cigarettes daily.

Q: Turning your attention to U.S. Exhibit 50615, can you identify that exhibit?

A: Yes. U.S. Exhibit 50615 is the paper that Trichopoulos published in 1981, entitled "Lung Cancer and Passive Smoking," 27 *International Journal of Cancer*, 1-4 (1981), based on a case-control study in Greece.

Q: Directing your attention to U.S. Exhibit 17201 entitled, "Greek Case-Control Study, Second Hand Smoke and Lung Cancer: Women," would you please describe that study for the Court?

A: Trichopoulos and his colleagues reported increased lung cancer risk in nonsmoking women married to cigarette smokers compared with nonsmoking women married to nonsmoking men. The investigators conducted a case-control study in Athens, Greece, which included cases and controls with a diagnosis other than for orthopedic disorders. They compared smoking by the husbands of cases and controls. The exhibit shows increased risk for those married to a smoker,\; that is, the relative risk of lung cancer increases as the amount of cigarettes that are smoked by the husband increases. The results demonstrate this dose-response relationship: nonsmoking women married to former smokers had a relative risk of 1.75; nonsmoking women married to men smoking 1-20 cigarettes per day had a relative risk of 2.5; and those married to men who smoked more than one pack per day had a relative risk of 3.5. The positive findings reported in 1981 were unchanged with subsequent expansion of the study population and more refined consideration of potential confounding, including diet.

Q: Have you reviewed these studies as part of your investigation in this matter?

A: Yes.

Q: Do these studies form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider these articles to be reliable authorities in the published scientific literature?

A: Yes.

Q: Doctor, is an association between passive smoking and lung cancer biologically plausible?

A: Yes. The association of involuntary smoking with lung cancer derives biological plausibility from the presence of carcinogens in sidestream smoke and the lack of a documented threshold dose for respiratory carcinogens in active smokers. Experimental exposure of non-smokers to secondhand smoke leads to their excreting NNAL, a tobacco-specific carcinogen, in their urine in comparison with unexposed nonsmokers. This finding has now been verified in observational studies. Non-smokers exposed to secondhand smoke also have increased concentrations of adducts of tobacco-related carcinogens in their blood; adducts refer to the binding of these compounds to blood and tissue components.

Q: Have the results of the early studies by Hirayama and Trichopoulos been replicated by other researchers?

A: Yes. Much further epidemiologic research has now been carried out. Epidemiologists have directly tested the association between lung cancer and involuntary smoking utilizing conventional epidemiological designs: the case-control and cohort studies. The majority of these studies are of the case-control design.

Q: Did the 1981 reports of Hirayama and Trichopoulos receive criticism?

A: Yes. These studies were observational studies, which have inherent limitations and critics focus on these limitations, particularly when there may be substantial policy implications, as in studies of secondhand smoke and lung cancer. When these first studies on secondhand smoke and lung cancer were published, they received substantial criticism. Some of the criticism was organized by the tobacco industry. Critics raised questions in particular about misclassification of exposure and confounding. From the tobacco industry's own documents, we know that efforts were made to create and sustain an apparent scientific controversy concerning research on secondhand smoke.

Q: Where have subsequent studies been conducted?

A: The association between secondhand smoke and lung cancer in adults has been examined in investigations conducted in the United States and many other countries.

Q: Doctor, what were the first reviews to find a causal relationship between secondhand smoke and lung cancer?

A: By 1986, the evidence had mounted and three reports published in that year concluded that secondhand smoke was a cause of lung cancer. The International Agency for Research on Cancer of the World Health Organization IARC concluded in 1986 that "passive smoking gives rise to some risk of cancer." In its monograph on tobacco smoking, the agency supported this conclusion on the basis of the characteristics of sidestream and mainstream smoke, the absorption of tobacco smoke materials during involuntary smoking, and the nature of dose response relationships for carcinogenesis.

In the same year, the National Research Council (NRC), Committee on Passive Smoking and the U.S. Surgeon General also concluded that involuntary smoking increases the occurrence

of lung cancer in nonsmokers. In reaching this conclusion, the NRC cited the biological plausibility of the association between exposure to secondhand smoke and lung cancer and the supporting epidemiological evidence. Based on a pooled analysis of the epidemiological data adjusted for bias, the report concluded that the best estimate for the excess risk of lung cancer in nonsmokers married to smokers was 25%.

The 1986 report of the Surgeon General characterized involuntary smoking as a cause of lung cancer in nonsmokers. This conclusion was based on the extensive information already available on the carcinogenicity of active smoking, on the qualitative similarities between secondhand smoke and mainstream smoke, and on the epidemiological data on involuntary smoking.

Q: After these 1986 reports, what other reviews found a causal relationship between secondhand smoke and lung cancer?

A: In 1992, the U.S. Environmental Protection Agency published its risk assessment of secondhand smoke as a carcinogen. The agency's evaluation drew on the toxicological evidence on secondhand smoke and the extensive literature on active smoking. A meta-analysis of the 31 studies published to that time was central in the decision to classify secondhand smoke as a class A carcinogen - namely a known human carcinogen. The meta-analysis considered the data from the epidemiologic studies by tiers of study quality and location, and used an adjustment method for misclassification of smokers as never-smokers. Overall, the analysis found a significantly increased risk of lung cancer in never-smoking women married to smoking men; for the studies conducted in the United States, the estimated relative risk was 1.19 (90% CI: 1.04, 1.35). Critics of the report raised a number of concerns including the use of meta-analysis, and some of the statistical details of the meta-analysis. The report, however, was endorsed by the Agency's

Science Advisory Board on which I served and its conclusion is fully consistent with the 1986 reports as well as other subsequent conclusions.

Q: Doctor Samet, turning your attention to U.S. Exhibit 63709, U.S. Exhibit 63708, U.S. Exhibit 64066, and U.S. Exhibit 88645, would you identify those exhibits?

A: U.S. Exhibit 63709 is the 1986 Report of the U.S. Surgeon General, U.S. Exhibit 63708 is the 1986 Report of The NRC Committee on Passing Smoking, U.S. Exhibit 64066 is the 1986 report from IARC, and U.S. Exhibit 88645 is the 1992 EPA Risk Assessment that I referenced.

Q: Did you review these reports as part of your investigation in this case?

A: Yes.

Q: Do the conclusions in these reports form part of the basis of the opinions that you hold in this case?

A: Yes.

Q: Are the reports reliable authorities in the scientific literature*?*

A: Yes.

Q: Since the EPA published its risk assessment in 1992, have other important studies been reported and published?

A: There have been several subsequent important additions to the literature. Most notable are the reports from Fontham, E. et al., "Environmental tobacco smoke and lung cancer in nonsmoking women: A Multicenter Study," 271(22) *JAMA* 752-59 (1994) and the 1997 meta-analysis of A.K. Hackshaw, M.R. Law, & N.J. Wald, "The accumulated evidence on lung cancer and environmental tobacco smoke," *British Medical Journal*, 315: 980-988 (1997).

Q: Doctor, turning your attention to JD 4719, what is this publication?

A: This is the publication by Fontham and colleagues that I address above.

Q: Directing your attention to U.S. Exhibit 17202, would you please explain what this exhibit summarizes to the Court?

A: This exhibit summarizes the multicenter U.S. study of Fontham and colleagues, JD 4719. This is the largest case-control study to date with 651 cases and 1253 controls, and it showed a 26% increase in lung cancer for nonsmokers married to smokers. This study also found a significant risk associated with occupational exposure to secondhand smoke. Nearly a doubling of relative risk was found where there was an occupational exposure to secondhand smoke over more than thirty years duration.

Q: How recently have studies been systematically evaluated?

A: There is substantial epidemiological evidence linking involuntary smoking to lung cancer and this evidence has been periodically evaluated and pooled using the technique of meta-analysis. This was done as recently as 2004 with the finding of 1.23 as the relative risk of lung cancer in never-smoking women married to ever smokers compared to never-smoking women married to never smokers, an excess risk of 23%.

Q: What is U.S. Exhibit 20599?

A: That is the report by Hackshaw that I described above.

Q: Directing your attention to U.S. Exhibit 17168 (JS101.2) entitled, "Meta-analysis of studies on Secondhand Smoke and Lung Cancer: Women," would you please explain to the Court what this exhibit summarizes?

A: Yes. This exhibit summarizes the report by Hackshaw and his colleagues, U.S. Exhibit 20599, that was updated in the IARC Monograph that was published in 2004. Hackshaw conducted a meta-analysis of 37 published studies. The excess risk of lung cancer for non-smoking women married to smokers was estimated at 24%. Adjustment for potential bias and

confounding by diet did not alter the estimate. This meta-analysis supported the 1998 conclusion of the United Kingdom's Scientific Committee on Tobacco and Health that secondhand smoke is a cause of lung cancer. This meta-analysis was updated by the epidemiologists who prepared the IARC monograph that was published in 2004.

Q: Directing your attention to U.S. Exhibit 17167 (JS101.1) entitled, "Meta-analysis of studies on Secondhand Smoke and Lung Cancer: Men," would you please explain to the Court what this exhibit summarizes?

A: Like U.S. Exhibit 17168, this is an updated meta-analysis that is reported in the IARC monograph that was published in 2004. In this instance the exhibit summarizes the results of nine case-control studies and two cohort studies examining lung cancer risk among nonsmoking men. This analysis reported that among nonsmoking men who lived with a smoker, the risk of lung cancer was increased by 37%.

Q: Did you review these publications as part of your investigation in this case?

A: Yes.

Q: Do these publications form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider these publications to be reliable authorities in the published scientific literature?

A: I do.

Q: Are you aware of any studies that have not found an association between passive smoking and lung cancer?

A: Yes. From time to time, studies are published that do not find a statistically significant association between secondhand smoke exposure and lung cancer risk. We expect such studies to be reported, as some are likely not to find significant results just by chance.

Q: Directing your attention to U.S. Exhibit 65086, what is that paper?

A: This exhibit is a 2003 paper in the *British Medical Journal* by Enstrom and Kabat that did not find an association. However, this study had a number of biases, including not carefully tracking the active smoking and secondhand smoke exposures of the study participants over time. When the 2002 meta-analysis carried out by IARC was redone in 2004 to include this study, the positive findings were unchanged.

Q: Do you know if the researchers in U.S. Exhibit 65086, Enstrom and Kabat, were funded by the tobacco industry?

A: Yes. The study was funded in part by the Center for Indoor Air Research, which was an organization created and funded by members of the tobacco industry.

Q: Turning your attention to U.S. Exhibit 17304 entitled, "Conclusions on Disease and Adverse Health Effects Caused by Secondhand Smoke," please identify the dates that governmental agencies and public health organizations concluded that secondhand smoke exposure causes lung cancer in adults.

A: As shown in this exhibit, the 1986 Surgeon General's Report concluded that secondhand smoke exposure causes lung cancer in adult nonsmokers. In 1992, the EPA concluded that "ETS" is a human carcinogen. Thereafter, in 1997, the California Environmental Protection Agency concluded that secondhand smoke is causal risk factor for lung cancer in adults, while the United Kingdom's Scientific Committee on Tobacco and Health reached the same conclusion

in 1998. Finally, in 2002, IARC concluded that secondhand smoke exposure is a causal risk factor for lung cancer in nonsmoking adults.

Q: What is U.S. Exhibit 76125?

A: This exhibit is the 1997 report of the California Environmental Protection Agency that concluded that secondhand smoke is causal risk factor for lung cancer in adults, as I mentioned previously.

Q: What is U.S. Exhibit 64063?

A: This exhibit is the 1998 report of the United Kingdom's Scientific Committee on Tobacco and Health that I mentioned previously.

Q: What is U.S. Exhibit 86746?

A: This exhibit is the 2002 IARC monograph that was published in 2004, concluding that secondhand smoke exposure is a causal risk factor for lung cancer in nonsmoking adults, as I mentioned before.

Q: Did you review these publications as part of your investigation in this case?

A: Yes.

Q: Do these publications form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider these publications to be reliable authorities in the published scientific literature?

A: I do.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do

you have an opinion to a reasonable degree of scientific certainty that exposure to secondhand smoke causes lung cancer in adults?

A: Yes, secondhand smoke exposure causes lung cancer in nonsmoking adults.

Q: Upon what do you base your opinion?

A: As I addressed in my testimony on active smoking, cigarette smoke contains carcinogens and inhaling smoke causes cancer. We have no scientific evidence to postulate that there is a level of smoke exposure that does not increase lung cancer risk. On this basis alone, including our knowledge of the nature of the carcinogens in secondhand smoke and the evidence from active smokers, I conclude that exposure to secondhand smoke poses a significant health risk to nonsmokers. The association of involuntary smoking with lung cancer derives biological plausibility from the presence of carcinogens both in secondhand smoke and in sidestream smoke, its main source, and from the lack of a documented threshold dose for respiratory carcinogens in active smokers.

In my opinion, therefore, the question is not whether secondhand smoke poses a risk; rather, the question is how much of a risk does secondhand smoke pose. That question has been studied by epidemiologists and public health officials over the past three decades, and they have quite consistently shown and concluded that secondhand smoke causes disease, including lung cancer, in nonsmokers. Those findings would be expected, as secondhand smoke contains the same irritants, toxicants, and carcinogens that are found in sidestream and mainstream smoke, and biomarkers of tobacco smoke, such as cotinine and the carcinogen NNAL, show that secondhand smoke is absorbed by non-smokers.

Overall, one of the most commonly studied exposures, being married to a smoker, increases lung cancer risk by about 20% compared to marriage to a nonsmoker.

Q: Doctor Samet, you stated above that the epidemiological studies examining the association between passive smoking and lung cancer use case-control and cohort designs, please explain to the Court the difference between case-control and cohort studies when examining this association.

A: In a case-control study, the exposures to secondhand smoke of nonsmoking persons with lung cancer are compared to those of an appropriate nonsmoking control group. In a cohort study, the occurrence of lung cancer over time in nonsmokers is assessed in relation to involuntary tobacco smoke exposure.

Q: Are there criticisms regarding the accuracy of these methodologies?

A: As I testified earlier, observational studies are subject to certain biases. The results of both study designs may be affected by inaccurate assessment of exposure to secondhand smoke, by inaccurate information on personal smoking that leads to classification of smokers as nonsmokers, by failure to assess and control for potential confounding factors, and by the misdiagnosis of a cancer at another site as a primary cancer of the lung.

In addition, one problem that has been raised is that interviews with a surviving spouse may be carried out to determine the smoking of a deceased study participant. There has been concern about the accuracy of such interviews. Methodological investigations suggest that sufficiently accurate information can be obtained by interview in an epidemiological study on the smoking of a spouse (i.e., never or ever smoker). However, information concerning quantitative aspects of the spouse's smoking is reported with less accuracy.

Another potential problem is that participants may be misclassified as never smokers, even when they did smoke in the past. Misclassification of current or former smokers as never smokers may introduce a positive bias because of the concordance of spousal smoking, that is,

smokers tend to marry other smokers. The extent to which this bias explains the numerous reports of association between spouse smoking and lung cancer has been considered and found to be an insufficient basis for explaining the association of spouse smoking with lung cancer.

Q: Doctor Samet, you mentioned "confounding." What potential confounders have critics focused their attention on?

A: As I stated in my testimony on active smoking, confounding takes place when the effect of the factor under study, e.g., secondhand smoke, becomes mixed with (or confounded by) the effect of another factor.

Critics of the findings on secondhand smoke and lung cancer have argued that uncontrolled confounding by lifestyle, occupation or other factors may explain the association. In fact, current data for the United States do indicate a generally less healthy lifestyle in those with greater secondhand smoke exposure. However, other than a few occupational exposures at high levels, as well as indoor radon, risk factors for lung cancer in never smokers that might confound the secondhand smoke association cannot be offered. Additionally, the relevance of these current studies to the published epidemiological studies of past exposures is uncertain and the association has been widely replicated. Thus, confounding cannot explain the consistent findings by researchers over the past 25 years that secondhand smoke is associated with lung cancer.

Q: Based on your training and experience as an epidemiologist and medical doctor and your review of the scientific literature on passive smoking, do the criticisms that you mentioned affect the scientific reliability or validity of the case-control and cohort studies that have found a causal relationship between passive smoking and lung cancer?

A: No. There has been repeated and careful exploration of these methodological issues, including confounding and exposure misclassification as artifactually producing the association of secondhand smoke with lung cancer risk. Repeatedly these potential sources of biases have been set aside. Additionally, the epidemiological data need to be interpreted within the context set by the very extensive information on the nature of secondhand smoke and the epidemiological evidence on active smoking. For active smokers, even the lowest levels of smoking on a daily basis are associated with increased risk.

Q: Approximately how many people each year in the United States die from lung cancer?

A: The total number of lung cancer deaths in the United States is about 160,000; there are slightly more new or incident cases, about 170,000 annually.

Q: Have estimates been made on how many of those deaths are attributable to secondhand smoke exposure?

A: Estimates suggest that around 3,000 of the lung cancer deaths in the United States are attributable to secondhand smoke. There are perhaps 10,000 lung cancer cases annually in never smokers, so that approximately 30% of these cases may result from passive smoking.

Q: Please identify the research that estimates that 3,000 lung cancer deaths are attributable to secondhand smoke exposure.

A: The number of lung cancer cases attributable to passive smoking is not subject to direct measurement so that indirect estimation approaches are needed. These are based on extrapolating risks measured in epidemiological studies to the population exposed to secondhand smoke. Estimates have also been based on the doses of carcinogens inhaled by involuntary smokers.

Starting in the 1990s, researchers have reviewed the published risk assessments of lung cancer and passive smoking and estimated the numbers of lung cancer cases in U.S. nonsmokers attributable to passive smoking. In one study by Repace and Lowery, the range of estimates, covering both never smokers and former smokers, was from 58 to 8124 lung cancer deaths for the year 1988, with an overall mean of 4500 or 5000 excluding the lowest estimate of 58. The bases for the individual estimates included the comparative dosimetry of tobacco smoke in smokers and nonsmokers using presumed inhaled dose or levels of nicotine or cotinine, the epidemiological evidence, and modeling approaches.

The 1992 estimate of the Environmental Protection Agency, based on the epidemiologic data, was about 3000, including 1500 and 500 deaths in never-smoking women and men, respectively, and about 1000 deaths in long-term former smokers of both sexes.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, what is your opinion to a reasonable degree of scientific certainty on the accuracy of estimated 3,000 annual lung cancer deaths caused by passive smoking?

A: Such estimates are based in the method of risk assessment and of necessity require assumptions and are inherently uncertain. I was on the EPA Scientific Advisory Board when the EPA issued its risk assessment. Nonetheless, they offer a useful indication of the magnitude of the risk, and certainly the number of estimated deaths is substantial, even though overshadowed by the enormous number of lung cancer deaths caused by active smoking. However, when compared with mortality figures in the United States in 2001 from malignant neoplasm of the skin, which accounted for 7,542 deaths, and from cervical cancer, which accounted for 4,092 deaths, the figures are significant.

Q: Doctor, what is the general prognosis for people with lung cancer?

A: As I testified earlier, prognosis for lung cancer is poor, with about 14% of patients surviving five years after diagnosis, and there has been little improvement in survival in recent decades. The majority of cases are too advanced for surgery when they present. Even after surgery to remove lung cancer, a mere 15-30% survive five years after diagnosis.

Q: Is there a basis for considering that passive smoking is associated with cancers other than lung cancer?

A: Yes. There is a basis for considering that secondhand smoke exposure might cause other types of cancer, but there have been relatively few studies to date and the findings are not convincing. For example, Hirayama reported significantly increased mortality from nasal sinus cancers and from brain tumors in nonsmoking women married to men in the Japanese cohort previously addressed. Cervical cancer, which has been linked to active smoking, was associated with duration of involuntary smoking in a case-control study in Utah. Some studies have addressed breast cancer and passive smoking.

Q: Do these studies have biological plausibility?

A: Certainly the organs of passive smokers, other than the lungs, are exposed to tobacco smoke carcinogens, just as with active smokers. Thus, there is a biological basis for considering that passive smoking might cause cancer at some of the other sites, for which active smoking is also a cause of cancer. It is not reasonable to consider that involuntary smoking is likely to be a cause of cancer for sites for which the much higher doses received by active smokers do not cause cancer. Breast cancer is an example of such a site. The International Agency for Research on Cancer has concluded that effects would not be produced in passive smokers that would not be produced to a larger extent in active smokers.

Q: Doctor, let's turn our attention to coronary heart disease now. Are there epidemiological studies that address the effect of passive smoking on coronary heart disease?

A: Yes. The epidemiological literature on passive smoking and heart disease goes back several decades. Cohort studies assessing the association between secondhand smoke and fatal CHD outcomes have demonstrated an increase in risk. For example, in 1984, in the cohort study of nonsmoking Japanese women, Hirayama demonstrated an increase in risk for death from ischemic heart disease in nonsmoking women married to husbands who smoked. In 1985, in a cohort study based in San Diego, Garland and colleagues demonstrated an increase in relative risk for death from ischemic heart disease from spousal secondhand smoke exposure of 3.6 where the spouse was a former smoker, and 2.7 where the spouse was a current smoker.

Q: What are some additional studies that have found an association between secondhand smoke exposure and coronary heart disease?

A: In a report by Humble and colleagues in 1990, passive smoking was found to increase the relative risk of cardiovascular death to 1.59 in nonsmoking participants in an Evans County, Georgia, cohort study.

Additionally, several large cohort studies have been conducted that address both fatal and nonfatal coronary heart disease outcomes and secondhand smoke exposure. These studies include analyses of large, national cohorts such as the Nurses' Health Study, the American Cancer Society Cancer Prevention Study I and II (CPS-I and CPS-II), and the Multiple Risk Factor Intervention Trial (MRFIT). Except for the analyses of CPS I and CPS II presented by LeVois and Layard in 1995, all other studies have demonstrated at least a modest increase in risk for fatal and nonfatal CHD due to secondhand smoke exposure.

Q: Doctor Samet, what is U.S. Exhibit 28521?

A: That exhibit contains the results of a study of 32,046 women 36 to 61 years of age by Ichiro Kawachi and his colleagues, entitled "A Prospective Study of Passive Smoking and Coronary Heart Disease," published in *Circulation* on May 20, 1997. The study was based on the participants in the Nurses' Health Study. Adjusting for a wide variety of CHD risk factors, any secondhand smoke exposure was associated with a relative risk of 1.71, occasional secondhand smoke exposure with a relative risk of 1.56, and regular secondhand smoke exposure with a relative risk of 1.97 for total CHD.

Q: Directing your attention to U.S. Exhibit 17200, which is titled "Relative Risks of Total Incident Coronary Heart Disease According to Duration of Adult Life Spent Living with a Smoker: Women," would you please explain what that exhibit summarizes to the Court?

A: This exhibit summarizes the results contained in the article by Kawachi and colleagues. The report assessed both fatal CHD and nonfatal myocardial infarction due to secondhand smoke exposure at home and work in this very large cohort. This table shows relative risk based on duration of exposure. For those women who were exposed to secondhand smoke for 30 years or more the relative risk was 1.8 compared to women who had not been exposed at all.

Q: Have you reviewed that study as part of your investigation in this matter?

A: Yes.

Q: Does that study form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider the article a reliable authority in the published scientific literature?

A: Yes.

Q: Doctor Samet, what is U.S. Exhibit 64090?

A: That exhibit contains the results of a meta-analysis involving comparison of secondhand smoke exposure of persons with coronary heart disease compared to controls that was done by Jiang He and his colleagues, entitled "Passive smoking and the rise of coronary heart disease," that was published in *The New England Journal of Medicine* on March 25, 1999. He summarized the results of eight case-control studies and ten cohort studies examining the association between secondhand smoke exposure and coronary heart disease.

Q: Directing your attention to U.S. Exhibit 17171 (JS104), which is titled "Meta-Analysis of Studies of CHD and Secondhand Smoke," would you please explain what that exhibit summarizes to the Court?

A: Yes. This exhibit summarizes the results found in the 1999 paper by He and colleagues. The study covers the studies that I have discussed above as well as others that were conducted in a number of countries throughout the world, including the United States, England, Australia and New Zealand, Argentina, Italy, and China. The researchers found a positive association overall between passive smoking and coronary heart disease.

Q: Have you reviewed that study as part of your investigation in this matter?

A: Yes.

Q: Does that study form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider the article a reliable authority in the published scientific literature?

A: Yes.

Q: Doctor Samet, you testified earlier that except for the analyses of the CPS I and CPS II presented by LeVois and Layard in 1995, all other studies have demonstrated

at least a modest increase in risk for fatal and nonfatal CHD due to secondhand smoke exposure. Did the tobacco industry provide funding for the LeVois and Layard study?

A: Yes.

Q: Please describe LeVois and Layard's findings.

A: As I stated above, LeVois and Layard analyzed data from CPS-I and CPS-II. Males and females self-reported as never smokers were not found to be more likely to die from coronary heart disease as the level of exposure to secondhand smoke increased. However, a significant increase in risk with passive exposure was reported for former smokers. In 1996, Steenland and colleagues reported analyses on the same study data with the CPS-II cohort and conducted four different analyses on the data set. They found that nonsmoking men had a relative risk of 1.22 for ischemic heart disease (IHD) death when exposed to a current smoker. In fact, in all four analyses that they performed, significant positive associations were found for men currently exposed to secondhand smoke. The associations for women were not statistically significant.

The effect of involuntary smoking was also assessed among the nonsmoking male participants in the Multiple Risk Factor Intervention Trial (MRFIT) (Svendsen, et al., 1987); these men had been selected in 1973 to be in the upper 10-15% of risk for mortality for coronary artery disease, based on a score from the Framingham study. They were then randomized to a program of risk factor reduction or to a control group. In comparison to nonsmoking men married to nonsmokers, never smokers with smoking wives had increased relative risk for coronary heart disease of 2.11; fatal or nonfatal coronary heart disease event of 1.48; and death from any cause of 1.96. These relative risks showed little change when former smokers were included in the analysis or when adjustment was made for other risk factors for coronary heart disease.

Q: Doctor Samet, what is J.D. Exhibit 3037?

A: That exhibit is the report by Steenland and colleagues entitled, "Environmental Tobacco Smoke and Coronary Heart Disease in the American Cancer Society CPS-II Cohort," that was published in *Circulation* in 1996, which I referenced above.

Q: Is it biologically plausible that exposure to secondhand smoke is causally associated with coronary heart disease?

A: Yes. It is biologically plausible that passive smoking could also be associated with increased risk for coronary heart disease through the same mechanisms considered relevant for active smoking, although the lower exposures of the passive smoker to smoke components have raised questions regarding the relevance of the mechanisms cited for active smoking.

Q: What evidence supports biological plausibility of a causal relationship between passive smoking and coronary hearth disease in adults?

A: There is extensive evidence on active smoking and heart disease, knowledge of mechanisms, and epidemiological studies on passive smoking and heart disease in nonsmokers. A review by Glantz and Parmley in the early 1990s addressed the pathophysiological mechanisms by which passive smoking might increase the risk of heart disease. They suggested that passive smoking may promote atherogenesis; increase the tendency of platelets to aggregate and thereby promote thrombosis; reduce the oxygen-carrying capacity of the blood; and unfavorably alter myocardial metabolism, much as for active smoking and coronary heart disease. More recent evidence suggests that secondhand smoke exposure adversely affects the cells that line the blood vessels, referred to as the endothelium or endothelial cells. Experimental models involving exposure to animals have been developed, and in these models adverse effects comparable to those postulated for humans can be demonstrated.

A later publication by Glantz and Parmley reported on three separate experiments involving exposure of nonsmokers to secondhand smoke showing that passive smoking affects measures of platelet function in the direction of increased tendency toward thrombosis. But changes in these same types of assays of platelet function have not been consistently associated with active smoking. The researchers also propose that carcinogenic agents such as polycyclic aromatic hydrocarbons found in tobacco smoke promote atherogenesis by effects on cell proliferation. Atherogenesis narrows the coronary arteries and disrupts the integrity of their lining, increasing risk for blood clots to form.

Passive smoking may also worsen the outcome of an ischemic event in the heart, which is a period when the heart is not receiving enough oxygen; animal data have demonstrated that secondhand smoke exposure increases cardiac damage following an experimental myocardial infarction. Experiments on two species of animals (rabbits and birds) have demonstrated that not only does exposure to secondhand smoke at doses similar to exposure to humans accelerate the growth of atherosclerotic plaques through the increase of lipid deposits, but it also induces atherosclerosis.

In addition to its effects on platelets, passive smoke exposure affects the oxygen-carrying capacity of the blood. Even small increments, on the order of 1%, in the carboxyhemoglobin, may explain finding that passive smoking decreases the duration of exercise of patients with coronary heart disease. This is supported with evidence that cigarette smoking has been shown to increase levels of carbon monoxide in the spaces where ventilation is low or smoking is particularly intense.

Q: Turning your attention to U.S. Exhibit 17206, please explain to the Court the dates on which government agencies and public health organizations concluded that secondhand smoke exposure causes coronary heart disease.

A: In 1997, the California EPA concluded that secondhand smoke exposure is a causal risk factor for coronary heart disease in adults. Similarly, in 1998, the United Kingdom's Scientific Committee on Tobacco and Health made the same conclusion. Additionally, although not appearing on this exhibit, in 1992, the American Heart Association also concluded that passive smoking causes coronary heart disease.

Q: Have you reviewed these publications as part of your investigation in this matter?

A: Yes.

Q: Do they form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider these articles to be reliable authorities in the published scientific literature?

A: Yes.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty that secondhand smoke exposure is a cause of coronary heart disease in adults?

A: Yes, secondhand smoke exposure is a cause of coronary heart disease in nonsmoking adults

Q: Why do you have that opinion?

A: My opinion is based on three broad lines of evidence: knowledge of mechanisms, epidemiological studies of active smoking, and epidemiological studies of passive smoking that I specifically reference above.

Q: Doctor, let's turn now from your conclusion on lung cancer and coronary heart disease in adults to your examination of other respiratory health effects in adults. Has exposure to secondhand smoke been investigated as a cause of other respiratory conditions in adults?

A: Yes, secondhand smoke has been investigated as a factor that might cause respiratory symptoms, such as cough, in adults. Its effects on lung function have also been considered. Finally, because persons with asthma might be sensitive to tobacco smoke, it has been investigated as a trigger for asthma attacks in nonsmoking adults.

Q: Let's begin with respiratory symptoms. What does the epidemiological and other evidence show to date?

A: A number of studies have addressed associations of secondhand smoke with risk for the common respiratory symptoms: cough, phlegm production, wheezing, and shortness of breath. These symptoms are relatively uncommon in adults who do not smoke and who have otherwise healthy lungs. This literature is mixed, with some studies showing increased risk associated with exposure to secondhand smoke, whether at home or in the workplace, and others showing no association.

Q: Has the Surgeon General or other public health authorities examined this evidence?

A: The evidence has been considered in several reports, dating back to the 1986 Report of the U.S. Surgeon General. The evidence has not been comprehensively reviewed since the 1990s, when it was examined by the Scientific Committee on Tobacco and Health in the United

Kingdom and the California Environmental Protection Agency. These groups did not find the evidence sufficient to support a causal conclusion.

Q: Have studies been carried out on secondhand smoke exposure and level of lung function in adults?

A: Secondhand smoke exposure has been shown to adversely affect level of lung function in children. The evidence on adults is quite limited, including some cross-sectional studies and a few cohort or longitudinal studies. To date, these studies do not provide convincing evidence of an adverse effect of secondhand smoke exposure on lung function level in general in adults.

Q: Has secondhand smoke exposure been examined as a factor that might adversely affect persons with asthma?

A: Yes, secondhand smoke exposure and asthma have been examined using both experimental and observational approaches. In the experiments, persons with asthma have been exposed to secondhand smoke, at rather high levels in some of the studies. Additionally, observational studies have been carried out to determine whether exposure to secondhand smoke in "real-world" settings adversely affects persons with asthma.

Q: What have these studies shown?

A: The design of experiments for approaching the adverse effects of secondhand smoke on adults with asthma is difficult. Of course, it is impossible to disguise the nature of the exposure from the volunteers and unrealistically high levels of secondhand smoke have been used in some of the studies. Additionally, volunteers might select themselves to be in the study because they are particularly concerned, or perhaps not concerned, about the effects of secondhand smoke on their lungs. These data have not provided consistent evidence for an effect of secondhand smoke

exposure on adults with asthma, when such exposures are carried out on a relatively short-term basis.

Q: What about the observational studies?

A: The observational studies provide stronger evidence for an adverse effect. The evidence comes from studies in which persons with asthma have been tracked on a short-term basis and their clinical status examined in relation to secondhand smoke exposure. Additionally, in some studies, level of lung function has been examined in relation to reports of exposure.

Q: Has a causal conclusion been reached on passive smoking and asthma in adults?

A: No, to date, no group has yet reached such a conclusion, but the evidence has not been systematically reviewed for almost a decade. Respirable particles and some of the irritants in tobacco smoke would be expected to adversely affect the sensitive lungs of adults with asthma. Established guideless for asthma management recommend limiting exposure to secondhand smoke.

Q: Doctor Samet, let's turn our attention from adults to infants and children. Based on your training as an epidemiologist and medical doctor and your review of the published scientific literature, in your opinion, are there adverse health effects of secondhand smoke exposure to infants and children?

A: Yes. Numerous scientific groups have concluded that secondhand smoke exposure is causally associated with adverse health effects in infants and children, including Sudden Infant Death Syndrome (SIDS), acute respiratory illnesses, chronic respiratory symptoms, reduced lung function growth, exacerbation of asthma, and acute and chronic middle ear disease.

Q: What is U.S. Exhibit 64062?

A: That exhibit is the International Consultation on Environmental Tobacco Smoke (ETS) and Child Heath, Consultation Report that was issued by the World Health Organization, Division of Noncommunicable Diseases in 1999. It reviewed the evidence on the health effects of children's exposures to secondhand smoke and arrived at conclusions.

Q: Using U.S. Exhibit 17206, please identify when government agencies and public health organizations reached these conclusions.

A: Beginning in 1986, the United States Surgeon General and the National Research Council found parental smoking to be associated with adverse effects in children. Later reports found these associations to be causal. These reports include those from the Surgeon General in 1986, the National Research Council and Committee on Passive Smoking in 1986, the U.S. Environmental Protection Agency in 1992, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment in 1997, the United Kingdom's Scientific Committee on Tobacco and Health in 1998, and the World Health Organization in 1999.

Q: Have you reviewed these conclusions as part of your investigation in this matter?

A: Yes.

Q: Do these conclusions form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider these conclusions to be reliable authorities in the published scientific literature?

A: Yes.

Q: How are children exposed to secondhand smoke?

A: For the child, secondhand smoke exposure can begin before birth. Smoking by the mother leads to exposure of the fetus *in utero* as tobacco smoke components cross from the

maternal circulation into the fetal circulation. Exposure of nonsmoking mothers to secondhand smoke also leads to exposure to the fetus through the same pathway, but doses would be less than with active maternal smoking. After the child is born, the infant is primarily exposed at home, particularly from the smoking of parents, but the smoking of other household members may also be damaging. Of course, the child can also be exposed in other locations where smoking is allowed. In general, smoking is no longer allowed in childcare locations, but there may be exposure in home day care facilities.

Q: How are children tested for exposure to tobacco smoke?

A: There are a number of ways to test for exposure using the approaches that I described earlier. These range from questionnaires to biochemical measures. For example, cotinine can be measured in urine, blood, or saliva, and nicotine monitors can be placed directly on children or in the rooms where they spend time. These studies document the importance of exposures in the home.

Q: Doctor, let's direct our attention now to specific diseases. What is SIDS?

A: SIDS, or Sudden Infant Death Syndrome, is the sudden, unexpected death of an infant, without evidence of any fatal illness at autopsy. After congenital anomalies, SIDS is the most common cause of death among infants one month to one year old in the United States, accounting for 2,236 deaths in 2001.

Q: When was the association between maternal smoking and SIDS first reported?

A: The association between maternal smoking and SIDS was first reported in 1966, and since then, over 15 more studies have confirmed this association.

Q: What studies that have specifically addressed the association between SIDS and postnatal secondhand smoke exposure.

A: To date, 10 studies have been conducted to determine the association between SIDS and postnatal exposure to smoking by the mother, six studies have looked at the association between paternal smoking and SIDS, and four studies have assessed household smoke exposure and SIDS. While maternal smoking during pregnancy has been associated with SIDS, these studies measured the effect of maternal smoking after pregnancy, paternal smoking, and general household smoking. In many of these studies however, it is difficult to separate the effects of secondhand smoke exposure and of maternal smoking during pregnancy and after the child has been born.

Q: Using J.D. Ex. 23698, please describe the methodology and findings of this case-control study on secondhand smoke and SIDS.

A: This exhibit is a report by Hillary Sandra Klonoff-Cohen and her colleagues entitled, "The Effect of Passive Smoking and Tobacco Exposure Through Breast Milk on Sudden Infant Death Syndrome" that was published in *JAMA* on March 8, 1995.

In this study of both maternal smoking during pregnancy and postnatal secondhand smoke exposure from mother, father, live-in adults and day care providers, the researchers compared exposures of 200 infants who died of SIDS in Southern California between 1989 and 1992 with 200 controls.

Infants who died of SIDS were more likely to have been exposed to secondhand smoke from the mother (increased risk by 128 percent), the father (increased risk by 246 percent), other live-in adults (increased risk by 118 percent), or all sources (mother, father, live-in adult, or day care provider: increased risk by 250 percent). The effect was independent of the parents' age, educational level, maternal smoking during pregnancy, maternal recreational drug use, prenatal

care, and infant's routine sleep position, medical conditions at birth, birth weight, and breastfeeding status.

A dose-response relationship was seen, whereby the greater the number of cigarettes and total numbers of smokers to which the infant was exposed to after birth, the greater the risk of SIDS. For all sources of secondhand smoke exposure considered, risk of SIDS was greater when smoking was taking place in the same room as the infant compared with anywhere in the house.

Q: Has meta-analysis been used to characterize the relationship between secondhand smoke exposure and SIDS?

A: A number of investigators and reports have used meta-analysis to assemble the evidence on secondhand smoke exposure and SIDS. These include the United Kingdom's Scientific Committee on Tobacco and Health, which relied on a meta-analysis carried out by Anderson and Cook.

Q: Why is meta-analysis an appropriate tool for epidemiologists to use to ascertain the relative risk of SIDS for infants exposed to secondhand smoke?

A: SIDS is relatively uncommon and it is difficult to conduct single, very large studies. When studies do not have large sample sizes and the effect of an exposure, secondhand smoke in this instance, is not large, then a real public health problem may be overlooked because of the imprecision of small studies. Meta-analysis is a widely used and accepted approach for combining evidence so as to gain a more precise description of the association of one factor with another.

Q: Doctor, what is U.S. Exhibit 63671?

A: This is the meta-analysis carried out by Anderson and Cook found in their report entitled "Passive Smoking and Sudden Infant Death Syndrome: Review of the Epidemiological Evidence" that was published in *Thorax* in 1997.

Q: Please turn to U.S. Exhibit 17169 entitled "Meta-analysis of Studies Examining Effects on Sudden Infant Death Syndrome (SIDS) of Maternal Prenatal and Postnatal Smoking." Can you explain that exhibit to the Court?

A: This exhibit summarizes findings of Anderson and Cook. The evidence is clear, as documented in this meta-analysis, that maternal smoking increases the relative risk for SIDS. Because mothers who smoke during pregnancy almost always continue to smoke after pregnancy, it has been difficult to separate pre-natal and post-natal effects of smoking by the mother of risk for SIDS. Exposure to smoking by other family members, the father, or others, has been associated with increased risk for SIDS in some, but not all, studies.

Q: Using U.S. Exhibit 17206, have government agencies and public health officials reached causal conclusions regarding exposure to maternal smoking and SIDS?

A: Yes. The literature on the causal association between SIDS and passive smoking is well established. Both the World Health Organization and the United Kingdom's Scientific Committee on Tobacco and Health have concluded that maternal smoking causes SIDS.

Q: Have you reviewed these conclusions as part of your investigation in this matter?

A: Yes.

Q: Do these conclusions form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider these conclusions to be reliable authorities in the published scientific literature?

A: Yes.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty that secondhand smoke exposure causes SIDS?

A: Yes, maternal smoking causes SIDS.

Q: Doctor Samet, let's turn now to acute respiratory illnesses in infants and children. What do we mean by acute respiratory illnesses in children and infants?

A: Generally, acute respiratory illnesses (ARI) in infants and children arise from respiratory infections, particularly with viruses. ARI includes the clinical syndromes of colds, croup, acute bronchitis, bronchiolitis, and pneumonia. Babies and young children have particularly high rates of ARIs ranging from approximately four to eight events per year, depending on definitions and methods of ascertainment. Very often, the illnesses are nonspecifically labeled as ARI, or as an upper respiratory tract illness or URI, or as a lower respiratory tract illness or LRI. Some viruses have been linked to particularly serious illnesses; for example, the respiratory syncytial virus causes bronchiolitis and the parainfluenza virus often causes croup.

Q: How do these illnesses impact the health of children?

A: These illnesses are common, particularly during the first year of life, and they are a substantial source of morbidity as well as absenteeism from school for the children and time lost from work for parents who take care of ill children. For the most severe illnesses, there is concern that there may be lasting consequences for lung health.

Q: Has secondhand smoke been investigated as a cause of ARI in infants and children?

A: Yes, ARI was among the first adverse health effects of secondhand smoke exposure to be investigated. As early as the late 1960s, epidemiological studies were beginning to show increased risk for such illnesses if the parents, particularly the mother, smoked. The early evidence suggested that secondhand smoke exposure was associated with more severe lower respiratory illness, such as bronchitis and pneumonia in particular. For example, one prospective cohort study in Israel showed that infants whose mothers smoked were more likely to be hospitalized for bronchitis and pneumonia between the ages of six and nine months old.

Q: What is the extent of the evidence on secondhand smoke exposure and acute respiratory illness?

A: There are now 30 years of research results on secondhand smoke exposure contained in numerous studies of varying designs, including cross-sectional, cohort, and case-control. Many have addressed the consequences of maternal smoking, but some have also considered smoking by fathers and others. Maternal smoking during pregnancy appears to affect the developing lung in a way that increases risk for more severe acute respiratory illnesses. Consequently, the studies of paternal smoking and smoking by other household members provide insights into the effects of secondhand smoke exposure after birth, without possible persistent effects of maternal smoking during pregnancy. There are now numerous studies on secondhand smoke and acute respiratory illness. A 1997 meta-analysis, for example, included 39 studies.

Q: Looking at U.S. Exhibit 17206, have government agencies and public health officials reached conclusions about a causal relationship between secondhand smoke exposure and ARI?

A: Yes, a causal conclusion has been reached by the California Environmental Protection Agency in 1997, the United Kingdom's Scientific Committee on Tobacco and Health in 1998, and the World Health Organization in its 1999 report.

Q: Have you reviewed these conclusions as part of your investigation in this matter?

A: Yes.

Q: Do these conclusions form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider these conclusions to be reliable authorities in the published scientific literature?

A: Yes.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty that secondhand smoke exposure causes ARI in children?

A: Yes, secondhand smoke exposure causes ARI in children.

Q: Doctor Samet, let's turn now to from ARI to chronic respiratory symptoms in children. What chronic respiratory symptoms in children are you referring to?

A: Children, just like adults, experience chronic, or persistent, respiratory symptoms. The major respiratory symptoms are cough, cough with phlegm production, wheezing, and shortness of breath. In adults these symptoms are causally associated with active cigarette smoking, while in children they are often a manifestation of asthma. They do occur, however, absent the presence of any underlying lung disease. Just as in adults, chronic respiratory symptoms affect well-being and quality of life for children.

Q: Have studies been carried out on chronic respiratory symptoms in children and exposure to secondhand smoke?

A: Numerous studies have been carried out on chronic respiratory symptoms and exposure to secondhand smoke, particularly from smoking by the parents. Much of the evidence comes from cross-sectional studies, which compare symptom rates in children of smoking parents with those in children of non-smoking parents. Fewer studies of the cohort or case-control design have been carried out.

Q: What evidence have these studies provided?

A: Most of the studies show increased occurrence of chronic respiratory symptoms in children whose parents smoke, particularly for those whose mother smokes. However, the literature shows that the smoking of the father is sufficient to produce chronic respiratory symptoms. Across the range of studies, a number of age groups and populations have been included. This diversity of the populations and the persistence of an effect of passive smoking with control for potential confounding factors suggest that the findings are reflective of underlying causal relationships.

Q: Have meta-analyses been undertaken on this topic?

A: Cook and Strachan reported the findings of a meta-analysis on this topic in 1997. Their review, which extended through April 1997, identified 60 relevant studies. The number of studies for the different respiratory symptoms was variable across wheeze, cough, phlegm, and shortness of breath.

Q: Looking at U.S. Exhibit 17206, have government agencies and public health officials reached conclusions about a causal relationship between secondhand smoke exposure with chronic respiratory symptoms?

A: Yes, the Surgeon General's report in 1986 found an association between chronic respiratory symptoms in children and the World heath Organization reached a causal conclusion in its 1999 report.

Q: Have you reviewed these conclusions as part of your investigation in this matter?

A: Yes.

Q: Do these conclusions form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider these conclusions to be reliable authorities in the published scientific literature?

A: Yes.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty that secondhand smoke exposure causes chronic respiratory symptoms in children and infants?

A: Yes, secondhand smoke exposure causes chronic respiratory symptoms in children and infants.

Q: Doctor Samet, what is the effect of secondhand smoke exposure on lung growth in children?

A: To answer this question it is important to have some understanding of how a child's lung grows. There are a number of critical phases of lung growth for children, beginning with gestation when the airways of the lung are being formed. At adolescence, as height increases, there is rapid, exponential growth of lung function until a plateau is reached by 16 to 18 years of age in girls and somewhat later in boys. The maximum level of lung function achieved

represents the plateau which defines the reserve available for people as they age. The natural lung function decline of aging is worsened by such factors as active cigarette smoking or occupational exposures. Numerous cross-sectional and cohort studies have been published since the late 1970s that examine the relationship of secondhand smoke exposure to various indices of lung function in children.

Q: How is a child's lung function measured?

A: There are a number of ways to measure lung function, depending on the age of the child. Complicated measurements can be made shortly after a child is born that provide insight into the resistance of the airways to airflow and also of the lung's size. Few studies have incorporated this measurement, which is relatively sophisticated and requires that the baby be administered a sleeping medication. However, the results of such studies show that even shortly after birth, infants whose mothers smoke during pregnancy have a lesser level of lung function than those whose mothers did not smoke during pregnancy.

Beginning about ages 5 or 6 years old, it is possible to measure a child's lung function using a spirometer, the same instrument used for adults. These machines, now primarily electronic, measure the rate at which air can be emptied from the lung and the amount of air that can be exhaled. These spirometric measures are used to assess the ventilation of the lung.

Q: What are the observed effects on lung function of exposure to secondhand smoke?

A: Numerous studies, beginning almost three decades ago, have shown lower lung function level in children whose parents smoked, compared to children whose parents did not smoke. As noted, maternal smoking during pregnancy adversely affects the child's airways, but continued effects of exposure after birth are well documented.

The evidence primarily comes from two types of studies: cross-sectional studies and cohort studies. In the cross-sectional studies, comparison has been made between the average lung function of exposed compared with non-exposed children. Many of these studies have been large, and the evidence is quite consistent in showing a several percentage point reduction of lung function in exposed children, compared with non-exposed children. In cohort studies, the actual rate of lung function growth has been tracked by carrying out spirometry periodically. These studies show that the rate of growth is lower in exposed children, compared with non-exposed children.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty that secondhand exposure causes reduction of lung function growth in otherwise healthy children?

A: Yes. The causal association between passive smoking and reduced lung function growth in children is well established. For example, the 1999 WHO consultation concluded that involuntary exposure to tobacco smoke causes reduced pulmonary function.

Q: Doctor Samet, what is asthma?

A: Asthma is a chronic respiratory condition characterized by airway inflammation, episodic airflow limitation, periodic attacks of wheezing, and difficulty in breathing, especially in expelling air. Asthma is caused by partial obstruction of the bronchi and bronchioles due to contraction of the muscles in the bronchial walls. While asthma attacks come and go there are wide variation in the degree of obstruction at different times. Asthma cannot be cured, but an attack can be relieved by treatment. In children, the diagnosis may be difficult to establish with full certainty, particularly in infants and young children.

Q: How common is asthma in children?

A: Asthma is quite common in school age children and is the most common chronic condition of childhood. The prevalence of asthma has been rising worldwide over the last decade for uncertain reasons. Asthma prevalence estimates in the United States are in the range of 8-10% in children.

Q: How does asthma impact the health of children?

A: Asthma has substantial adverse effects on children. Some children have a crippling disease and restricted activities while others may have only episodic wheezing and cough. Many need chronic medication. Asthma is an important cause of school absenteeism.

Q: How is asthma diagnosed in childhood?

A: The diagnosis of asthma in childhood can be difficult, particularly in infants and younger children. It is generally established on a clinical basis, particularly with a history of episodic wheezing and shortness of breath. Confirmatory lung function testing may be carried out. At younger ages, viral illnesses associated with wheezing are common; respiratory syncytial virus, for example, causes bronchiolitis (inflammation of the small airways of the lung) which produces wheezing. It may be difficult to differentiate an episode of bronchiolitis associated with secondhand smoke exposure from onset of childhood asthma. At later ages, the distinction between infection-induced wheezing and asthma is more readily made. At older ages, characteristically, the children have a background of allergy and there is often a family history. In these circumstances, secondhand smoke exposure and/or other factors may incite asthma in a child already at risk.

Q: Does secondhand smoke exposure cause the onset of new asthma cases?

A: For the reasons described above related to genetic predisposition and the difficulty of differentiating asthma from infection-induced wheezing, the answer to this question is not straightforward. Secondhand smoke exposure, particularly from smoking by the mother, increases risk for lower respiratory illnesses which trigger wheezing in children. Many of these children do not continue wheezing for lengthy periods, or permanently, and consequently may not have typical "asthma" but rather infection-induced wheezing. In children who are genetically predisposed to develop asthma, secondhand smoke exposures appear to be one of the triggers that incite symptoms and perhaps lead to earlier onset of symptoms. However, it is possible that some children will develop asthma once they have encountered any sufficient triggering, environmental stimulus.

Q: What studies have examined the relationship between secondhand smoke exposure and onset of asthma in children?

A: There have now been many studies on this question, which has not been readily investigated. There are a number of cohort studies which have followed children to determine predictors of asthma, including the role of secondhand smoke exposure. In general, the findings of these studies are consistent with my conclusions above.

Q: Have meta-analyses on childhood asthma been carried out?

A: Yes, the literature has been summarized by Strachan and Cook, both in regard to incidence of asthma and to prevalence of asthma. Comparisons of asthma incidence and secondhand smoke exposed and not exposed children can provide insights into the role of secondhand smoke exposure, particularly from smoking of parents, in causing onset of asthma. Studies of asthma prevalence provide some insights concerning incidence, one of the

determinants of prevalence, but also insights into the role of secondhand smoke exposure in terms of determining the severity of asthma.

Q: Please direct your attention to U.S. Exhibit 17170 (JS103), which is titled "Meta-Analysis of Asthma Prevalence in Children Where Either Parent Smokes." Would you explain what this exhibit summarizes to the Court?

A: Yes. This exhibit summarizes the results of a meta-analysis in the report by Cook and Strachan entitled "Parental smoking and prevalence of respiratory symptoms and asthma in school age children" that was published in *Thorax* in 1997. Overall, they found evidence for a 30% increased risk of chronic respiratory symptoms associated with parental smoking. There was an approximately 20% increase in asthma prevalence, comparing children exposed to parental smoking to unexposed children. Increased risk persisted with adjustment for potential confounding factors. Since then, there have been further reports of studies on this topic, but a further meta-analysis has not yet been reported.

Strachan and Cook also reviewed studies of asthma incidence of the cohort and case-control designs. They found a small increase in incidence associated with exposure, but interpreted the pattern of findings, particularly by age, as implicating smoking more as a trigger than as an etiologic factor. Research is ongoing on this issue.

Q: What do the studies show with regard to indicators of asthma severity?

A: For asthma severity, the evidence is quite consistent in showing greater disease severity in children with asthma who are exposed to secondhand smoke. In fact, general clinical recommendations call for parents of children with asthma to not smoke in their presence.

Q: Looking at U.S. Exhibit 17206, have government agencies and public health officials reached conclusions about a causal relationship between secondhand smoke exposure and childhood asthma?

A: The most recent conclusions on this topic come from the 1997 report of the California Environmental Protection Agency, the 1998 report of the United Kingdom's Scientific Committee on Tobacco and Health, and from the 1999 consultation on secondhand smoke carried out by the World Health Organization. Each of these groups concluded that secondhand smoke exposure is a cause of exacerbations or more severe disease in children with asthma. The California report also concluded that secondhand smoke exposure is a risk factor for "induction of new cases of asthma." The other reports noted that secondhand smoke exposure produces symptoms but does not cause the underlying tendency to develop asthma.

Q: Have you reviewed these conclusions as part of your investigation in this matter?

A: Yes.

Q: Do these conclusions form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider these conclusions to be reliable authorities in the published scientific literature?

A: Yes.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty that exposure to secondhand smoke causes asthma exacerbation and symptoms in children.

A: Yes. As I stated above, the literature on this subject is well established. Exposure to secondhand smoke causes asthma exacerbation and symptoms in children.

Q: What kinds of ear problems do infants and young children have?

A: Of course, ear problems are common among infants and young children. The most prevalent include acute otitis media, generally thought to be caused by infectious agents, and chronic otitis, sometimes referred to as chronic serous otitis or "glue ear." Children with these chronic ear problems often have difficulty hearing and may require substantial medical treatments, including surgery.

Q: Has secondhand smoke exposure been associated with increased risk for ear problems in infants and young children?

A: Yes, there have been many reports on both acute and chronic ear problems, showing associations of these problems with smoking by the parents.

Q: What is U.S. Exhibit 63,634?

A: This exhibit is a report by Strachan and Cook entitled, "Parental Smoking, middle ear disease and Adenotonsillectomy in Children," published in *Thorax* in 1998. It is a meta-analysis of parental smoking and middle ear disease, as well as on removal of the adenoids and tonsils. They identified 18 studies of acute otitis media, nine of recurrent otitis media, five of middle ear effusion, nine on surgery for "glue ear," and four on removal of the tonsils and adenoids.

Q: What did this meta-analysis show?

A: The evidence was consistent in showing increased risk for middle ear disease, regardless of the outcome measure used—recurrent otitis media, middle ear effusion, or inpatient or outpatient treatment for "glue ear." Strachan and Cook did not pool the evidence for acute otitis

media because of the variety of studies, but noted that most showed an increased risk for acute otitis media if either parent smoked.

Q: Is there a biological basis for considering that secondhand smoke might cause middle ear disease?

A: Yes, the middle ear is a delicate structure that is connected to the oral cavity through the Eustachian tube, which equalizes pressure between the middle ear and the oral cavity or atmosphere. Any irritation or inflammation of the Eustachian tube may lead to its closure and the possibility of development of middle ear problems. Secondhand smoke would be expected to deposit along the upper airway as air is inhaled, and the opening of the Eustachian tube would be exposed to secondhand smoke.

Q: Looking at U.S. Exhibit 17206, have public health authorities and government agencies reached any conclusion on secondhand smoke exposure and risk for middle ear disease?

A: Yes, the 1998 United Kingdom's Scientific Committee on Tobacco and Health and the World Health Organization's 1999 report on secondhand smoke both concluded that secondhand smoke exposure does cause middle ear disease.

Q: Have you reviewed these publications as part of your investigation in this matter?

A: Yes.

Q: Do these publications form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider these publications to be reliable authorities in the published scientific literature?

A: Yes.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty that exposure to secondhand smoke causes middle ear disease in children?

A: Yes. As I address above, the literature on this issue is well established. Exposure to secondhand smoke causes middle ear disease in children.

Q: Turning to U.S. Exhibit 17306 entitled "Diseases and Other Adverse Health Effects Caused by Secondhand Smoke." Can you explain this exhibit to the Court?

A: Yes. This exhibit summarizes all the diseases and other adverse health effects caused by exposure to secondhand smoke in adults and infants and children. For adults, causation has been established for lung cancer and coronary heart disease. For infants and children, causation has been established for SIDS, exacerbation of asthma, chronic respiratory symptoms, reduced lung function growth, middle ear disease, and acute respiratory illnesses.