

Comment Submissions - Proposed Adoption of Exposures to Listed Chemicals in Coffee Posing No Significant Risk

Published Name:

CERT's Submission No. 15 regarding the Opinions of Dr. Stephen M. Rappaport regarding No Threshold Linearity of Acrylamide/Glycidamide Adduct Formation.

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Post date:

08/15/2018 - 3:48pm

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August 15, 2018

*Via electronic submission to
<https://oehha.ca.gov/comments>*

Monet Vela
Office of Environmental Health Hazard Assessment
P.O. Box 4010
Sacramento, California 95812-4010

Re: Proposed Adoption of New Section Under Article 7: No Significant Risk Levels
Section 25704: Exposures to Listed Chemicals in Coffee Posing No Significant Risk

CERT'S SUBMISSION NO. 15

Dear Ms. Vela:

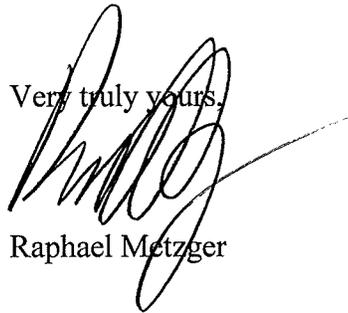
Enclosed herewith are the following documents that are being submitted on behalf of our client, the Council for Education and Research on Toxics (CERT) regarding the Opinions of Dr. Stephen M. Rappaport regarding No Threshold Linearity of Acrylamide/Glycidamide Adduct Formation:

1. Exhibit A - Opinions of Dr. Stephen M. Rappaport in CERT v. McDonald's case (August 16, 2007).
2. Exhibit B - ; Opinions of Dr. Stephen M. Rappaport in CERT v. Starbucks (April 14, 2014, but erroneously dated March 26, 2013).
3. Exhibit C - Critique of Dr. Swenberg's Acrylamide Mutation Threshold Hypothesis.
4. Exhibit D - Testimony of Stephen M. Rappaport in *CERT v. Starbucks* trial, October 1, 2014 a.m.
5. Exhibit E - Testimony of Stephen M. Rappaport in *CERT v. Starbucks* trial, October 1, 2014 p.m.

6. Exhibit F - Curriculum Vitae of Stephen M. Rappaport, Ph.D.

Kindly include these materials of Dr. Stephen M. Rappaport in the record for this rulemaking proceeding.

Very truly yours,

A handwritten signature in black ink, appearing to read 'Raphael Metzger', written over the typed name below.

Raphael Metzger

RM:ip
encls: as specified

EXHIBIT “A”

S. M. RAPPAPORT, Ph.D.

Consultant in Occupational and Environmental Health

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██████████ CA ██████████
U.S.A.

Tel.: 510/260-0202

August 16, 2007

I have the following opinions in the matter of CERT vs. McDonalds Corporation.

Abbreviations: AA, acrylamide; GA, glycidamide; Hb-AA, hemoglobin adduct of AA; Hb-GA, hemoglobin adduct of GA; AAMA, mercapturic acid of AA; GAMA, mercapturic acid of GA; N7-GA-Gua, N7 guanine DNA adduct of GA.

- 1. AA is formed from reactions between asparagine and sugars, such as fructose or glucose (Maillard reaction and other possible reactions). Foods that contain high levels of asparagine and sugars are sources of AA in the diet. Cigarette smoke also contains AA.**

Dybing et al. provide an extensive review of proposed reactions leading to formation of AA in foods (Dybing *et al.*, 2005). Potatoes have high concentrations of asparagine and sugars and thus are prominent sources of AA in western diets. The authors summarized FDA data, indicating that French fries and chips contained the highest levels of AA (median=318 µg/kg; *n* = 439) of 13 food groups. Their summary of EU data showed that French fries, potato chips, and potato fritters also had high AA levels (median=178-600 µg/kg; *n* = 3442). The authors concluded that the major food categories contributing to AA exposure in foods were "... French fries, potato chips, cereals, crispbread, bread, coffee, pies, and pastries." Estimated intake of AA from 9 countries varied with country and the population examined (age, gender) with mean values in the range of 0.2 – 1.3 µg/kg b.w./d.

In Sweden, a recent study estimated median AA intake was 53 µg/d (*n* = 35) for nonsmoking men and 38 µg/d (*n* = 35) for nonsmoking women (Wirfalt *et al.*, 2007). Very high levels of AA have been measured in cooked (especially fried) potatoes in Sweden (Tareke *et al.*, 2002).

- 2. AA is metabolized to GA, which produces DNA adducts. If AA exerts its carcinogenicity through a genotoxic mode of action, then GA is likely to be the ultimate carcinogen.**

AA is metabolized by two prominent pathways in mammals, namely, conjugation with GSH to produce AAMA and oxidation to GA via CYPs, primarily CYP2E1, to form GA.

GA-DNA adducts have been detected at the N7 position of guanine, the N1 position of adenosine, and the N3 position of adenine (reviewed by Tornqvist, et al., (2006)).

Increased levels of N7-GA-Gua have been reported in the livers of B6C3F1 mice and Fisher 344 rats dosed either with AA (0.1 mg/kg b.w.) or equimolar amounts of GA (Doerge *et al.*, 2005b; Doerge *et al.*, 2005c), relative to control animals. This is apparently the lowest dose level that has been tested for production of DNA adducts in experimental animals. The authors concluded that "...the total internal exposure to GA determines subsequent DNA adduct formation and that other metabolic or reactivity factors are not important... Furthermore, this comparison suggests that despite kinetic differences in the metabolism and disposition of AA between rats and mice, DNA adduct formation in liver is remarkably similar at the relatively low oral dose of 0.1 mg/kg AA." In rats and mice dosed with AA at 50 mg AA/kg b.w., the same laboratory detected N7-GA-Gua in the livers, lungs, kidney, leukocytes, and testis, at levels within about a factor of two of each other (Doerge *et al.*, 2005a). Other laboratories have also detected DNA adducts in animals dosed with AA (reviewed by (Tornqvist *et al.*, 2006)).

3. Substantial fractions of the AA and GA doses are bioavailable, following oral dosing of AA in animals or humans. This indicates that AA is readily absorbed from oral dosing and is rapidly metabolized to GA, both of which are efficiently distributed to tissues via the systemic circulation. Urinary levels of the mercapturic acids of AA and GA, i.e., AAMA and GAMA, serve as biomarkers of recent exposure and internal dose.

The landmark study of Miller *et al.* showed that ^{14}C -AA was absorbed within 1 h following oral administration (1, 10, and 100 mg/kg b.w.) and was distributed uniformly throughout the bodies of Fisher 344 rats (Miller *et al.*, 1982). AA was eliminated with biphasic kinetics with a rapid distribution phase (rate constant= 3.37 d^{-1}) and a slower terminal elimination phase rate constant= 0.225 d^{-1}). About 12% of the dose was retained in the blood, indicating that AA had been bound in the blood (sequestered in erythrocytes). Most of the elimination of AA occurred in the urine (71%), primarily as AAMA. Parent AA was eliminated quite rapidly (half life= 1.7 h) indicating that metabolism of AA was rapid and efficient.

Recent updates of Miller's study have documented the high bioavailability of both AA and GA following administration of AA to rats and mice. These newer studies have also reported an extensive set of biomarkers of AA and GA metabolism that emphasize the bioavailability of these compounds in all tissues (Doerge *et al.*, 2005b; Doerge *et al.*, 2005c).

In a single human subject to whom deuterium-labeled AA had been orally administered (13 $\mu\text{g/kg}$ b.w.), biphasic elimination kinetics were observed, similar to that in rats (Boettcher *et al.*, 2006b). Elimination half lives for AAMA and GAMA were about 3.5 h. After 2 d, 52% of the total dose had been eliminated in the urine indicating that at least 52% of the AA dose was bioavailable.

In a larger study of human volunteers, 6 German subjects received a meal containing potato chips (0.94 mg; 150 g of chips containing 6.23 $\mu\text{g AA/g}$) (Fuhr *et al.*, 2006). AA, AAMA and GAMA were continuously monitored in the urine. After 72 h, 60.3% of the dose had been recovered in the urine, indicating that at least 60.3% of the AA dose was bioavailable. These results are similar to those originally reported in rats (Miller *et al.*, 1982).

After reviewing experimental studies in various species, Dybing *et al.* concluded that the bioavailability was high in rats (68-90%), dogs (73%), miniature pigs (99%), and humans (34%) (Dybing *et al.*, 2005). (Note that this human estimate was based upon a single study).

Sorgel *et al.* measured AA in breast milk of two mothers who consumed a prepared diet high in AA from fried potatoes and other foods (Sorgel *et al.*, 2002). The same study also documented transfer of AA across fresh placentas in laboratory perfusion experiments.

4. AA and GA are electrophiles which bind to proteins, including Hb, to form adducts. These protein adducts can be used as dosimeters of AA exposure and biomarkers of internal dose of AA and GA over periods of months.

In summarizing background levels of Hb-AA in humans (measured as *N*-terminal valine adducts), Dybing *et al.*, reported mean levels ranging from 21 pmol/g globin to 40 pmol/g globin in 5 studies with between 5 and 25 subjects per study (Dybing *et al.*, 2005).

In rats and mice to which GA had been administered (i.p.) linear production of Hb-GA was observed in rats (dose range: 0-130 mg/kg b.w.) and mice (dose range: 0-61 mg/kg b.w.) (Paulsson *et al.*, 2003).

In rats to which AA had been administered (i.p.), levels of Hb-AA increased linearly with increasing AA dose (0-100 mg/kg b.w.) whereas levels of Hb-GA showed evidence of saturable metabolism of AA to GA, notably at doses above 10 mg/kg b.w. (note that these were Cys adducts of Hb) (Bergmark *et al.*, 1991). Metabolism appeared to be completely saturated at doses above 50 mg/kg b.w. Over the dosing range of 10-100 mg/kg b.w., the percentage of GA derived from AA decreased from

about 50% to about 15 %. This also reflects the saturation of metabolism in rats dosed with AA above 10 mg/kg b.w.

Fennell et al. administered ^{13}C -AA orally to groups of 6 healthy male human subjects at dose levels of 0.5, 1.0, and 3.0 mg/kg b.w. Levels of Hb-AA and Hb-GA were subsequently measured and found to be highly linear with the administered dose (Fennell *et al.*, 2005).

Using a steady-state level of 30 pmol Hb-AA/g globin (the average amount observed in human background studies) Dybing et al., estimated an uptake rate of 1.1 $\mu\text{g}/\text{kg b.w.}/\text{d}$ (Dybing *et al.*, 2005).

5. Based upon ratios of Hb-GA:Hb-AA and GAMA:AAMA reported in various human studies, the fraction of AA metabolized to GA in humans is probably in the range of 0.2 to 0.4, with considerable variability among subjects.

In 44 nonsmoking Norwegian subjects with background exposures to AA, the median ratio of Hb-GA:Hb-AA was 0.49 (Bjellaas *et al.*, 2007a).

In 13 nonsmoking German subjects, the median ratio of Hb-GA:Hb-AA was 0.85 (Schettgen *et al.*, 2004). Levels of Hb-GA were highly correlated with levels of Hb-AA in these subjects, indicating the AA was the source of GA. In these same subjects the median ratio of levels of the urinary metabolites GAMA:AAMA was 0.22 (Boettcher *et al.*, 2005). The urinary levels of GAMA and AAMA were also highly correlated in these subjects.

Levels of Hb-AA and Hb-GA were measured as *N*-terminal valine adducts in three groups of 6 human volunteers receiving an oral dose of ^{13}C -AA (0.5, 1.0, or 3.0 mg/kg b.w.) (Fennell *et al.*, 2005). The ratios of Hb-GA:Hb-AA were 0.36, 0.38, and 0.44 in the respective dose groups.

In a single human subject to whom deuterium-labeled AA had been orally administered (13 $\mu\text{g}/\text{kg b.w.}$), the ratio of GAMA:AAMA was 0.1 (Boettcher *et al.*, 2006b).

In a study of 6 German volunteers fed AA in potato chips (0.94 mg), the mean ratio of GAMA:AAMA was 0.12 (Fuhr *et al.*, 2006).

In a study of 65 nonsmoking subjects in Norway, Bjellaas et al. reported a median molar ratio of 0.46 for GAMA:AAMA (Bjellaas *et al.*, 2005). The same group conducted an additional study of urinary metabolite levels in 46 nonsmoking Norwegian subjects where the median molar ratio of GAMA:AAMA was 0.06 (Bjellaas *et al.*, 2007b).

6. The internal doses of AA and GA increase with increasing levels of AA in foods. This indicates that, other than smoking, diet is a major source of the AA and GA doses in humans.

In Sweden, a significant linear regression was observed between AA in foods (from food frequency questionnaires) and levels of Hb-AA. Among nonsmoking men, significant correlation was observed between AA, from fried potatoes and French fries, and levels of Hb-AA (Hagmar *et al.*, 2005; Wirfalt *et al.*, 2007).

Boettcher et al. monitored levels of AAMA and GAMA in the urine of three German volunteers over two days of fasting (Boettcher *et al.*, 2006a). Levels of AAMA and GAMA declined during fasting and returned to baseline values after resumption of the normal diet; this indicates that the diet was the main source of AAMA and GAMA in these subjects.

In 46 nonsmoking Norwegian subjects, urinary levels of AAMA and GAMA increased after 24 h of fasting and resumption of a normal diet (Bjellaas *et al.*, 2005).

In 43 nonsmoking Norwegian subjects, levels of Hb-AA were significantly positively associated with dietary exposures to potatoes, potato chip, and crisp bread (levels estimated from food frequency questionnaires) (Bjellaas *et al.*, 2007a).

7. Given rapid uptake and distribution of AA in humans and rodents and apparent first-order metabolism of AA to GA in mammals at administered doses below about 5 - 10 mg/kg b.w.,

all toxicokinetic processes should be linear. This is consistent with a low-dose linear model for carcinogenicity, based upon a genotoxic mode of action where GA is the ultimate carcinogen.

In a separate document, I comment upon the report, "Evidence-Based Dose Response Assessment for Thyroid Tumorigenesis from Acrylamide via Oral Exposure," by Michael Dourson, et al. (letter to R. Metzger, July 1, 2007). In that document, I show that the thyroid tumor data from the rat bioassays conducted by Johnson et al. and Friedman et al. are consistent with a linear low-dose model. Since the highest dose groups in those bioassays were 2.0 – 3.0 mg AA/kg b.w./d, the kinetic processes leading to the production of the genotoxic metabolite GA should have been linear.

References

- Bergmark E, Calleman CJ, Costa LG. Formation of hemoglobin adducts of acrylamide and its epoxide metabolite glycidamide in the rat. *Toxicol Appl Pharmacol*, 1991; 111(2): 352-63.
- Bjellaas T, Janak K, Lundanes E, Kronberg L, Becher G. Determination and quantification of urinary metabolites after dietary exposure to acrylamide. *Xenobiotica*, 2005; 35(10-11): 1003-18.
- Bjellaas T, Olesen PT, Frandsen H, Haugen M, Stolen LH, Paulsen JE, et al. Comparison of estimated dietary intake of acrylamide with hemoglobin adducts of acrylamide and glycidamide. *Toxicol Sci*, 2007a; 98(1): 110-7.
- Bjellaas T, Stolen LH, Haugen M, Paulsen JE, Alexander J, Lundanes E, et al. Urinary acrylamide metabolites as biomarkers for short-term dietary exposure to acrylamide. *Food Chem Toxicol*, 2007b; 45(6): 1020-6.
- Boettcher MI, Schettgen T, Kutting B, Pischetsrieder M, Angerer J. Mercapturic acids of acrylamide and glycidamide as biomarkers of the internal exposure to acrylamide in the general population. *Mutat Res*, 2005; 580(1-2): 167-76.
- Boettcher MI, Bolt HM, Angerer J. Acrylamide exposure via the diet: influence of fasting on urinary mercapturic acid metabolite excretion in humans. *Arch Toxicol*, 2006a.
- Boettcher MI, Bolt HM, Drexler H, Angerer J. Excretion of mercapturic acids of acrylamide and glycidamide in human urine after single oral administration of deuterium-labelled acrylamide. *Arch Toxicol*, 2006b; 80(2): 55-61.
- Doerge DR, da Costa GG, McDaniel LP, Churchwell MI, Twaddle NC, Beland FA. DNA adducts derived from administration of acrylamide and glycidamide to mice and rats. *Mutat Res*, 2005a; 580(1-2): 131-41.
- Doerge DR, Young JF, McDaniel LP, Twaddle NC, Churchwell MI. Toxicokinetics of acrylamide and glycidamide in B6C3F1 mice. *Toxicol Appl Pharmacol*, 2005b; 202(3): 258-67.
- Doerge DR, Young JF, McDaniel LP, Twaddle NC, Churchwell MI. Toxicokinetics of acrylamide and glycidamide in Fischer 344 rats. *Toxicol Appl Pharmacol*, 2005c; 208(3): 199-209.
- Dybing E, Farmer PB, Andersen M, Fennell TR, Lalljie SP, Muller DJ, et al. Human exposure and internal dose assessments of acrylamide in food. *Food Chem Toxicol*, 2005; 43(3): 365-410.
- Fennell TR, Sumner SC, Snyder RW, Burgess J, Spicer R, Bridson WE, et al. Metabolism and hemoglobin adduct formation of acrylamide in humans. *Toxicol Sci*, 2005; 85(1): 447-59.
- Fuhr U, Boettcher MI, Kinzig-Schippers M, Weyer A, Jetter A, Lazar A, et al. Toxicokinetics of acrylamide in humans after ingestion of a defined dose in a test meal to improve risk assessment for acrylamide carcinogenicity. *Cancer Epidemiol Biomarkers Prev*, 2006; 15(2): 266-71.
- Hagmar L, Wirfalt E, Paulsson B, Tornqvist M. Differences in hemoglobin adduct levels of acrylamide in the general population with respect to dietary intake, smoking habits and gender. *Mutat Res*, 2005; 580(1-2): 157-65.
- Miller MJ, Carter DE, Sipes IG. Pharmacokinetics of acrylamide in Fisher-344 rats. *Toxicol Appl Pharmacol*, 1982; 63(1): 36-44.
- Paulsson B, Kotova N, Grawe J, Henderson A, Granath F, Golding B, et al. Induction of micronuclei in mouse and rat by glycidamide, genotoxic metabolite of acrylamide. *Mutat Res*, 2003; 535(1): 15-24.
- Schettgen T, Rossbach B, Kutting B, Letzel S, Drexler H, Angerer J. Determination of haemoglobin adducts of acrylamide and glycidamide in smoking and non-smoking persons of the general population. *Int J Hyg Environ Health*, 2004; 207(6): 531-9.
- Sorgel F, Weissenbacher R, Kinzig-Schippers M, Hofmann A, Illauer M, Skott A, et al. Acrylamide: increased concentrations in homemade food and first evidence of its variable absorption from food, variable metabolism and placental and breast milk transfer in humans. *Chemotherapy*, 2002; 48(6): 267-74.

- Tareke E, Rydberg P, Karlsson P, Eriksson S, Tornqvist M. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. *J Agric Food Chem*, 2002; 50(17): 4998-5006.
- Tornqvist M, Paulsson.B., Osterman-Golkar S. Chapter 8, *Biomonitoring of acrylamide. In, Acrylamide and other hazardous compounds in heat-treated foods*. Cambridge, U.K.: Woodhead Publishing Ltd.; 2006.
- Wirfalt E, Paulsson B, Tornqvist M, Axmon A, Hagmar L. Associations between estimated acrylamide intakes, and hemoglobin AA adducts in a sample from the Malmo Diet and Cancer cohort. *Eur J Clin Nutr*, 2007.

EXHIBIT “B”

S. M. RAPPAPORT, Ph.D.

Consultant in Occupational and Environmental Health

**[REDACTED], CA
[REDACTED]
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Tel.: 510/334-8128

March 26, 2013

Mr. Raphael Metzger
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via E-mail www.toxictorts.com

Re: CERT v. Starbucks Corporation *et al.*

Dear Mr. Metzger:

I have summarized my professional qualifications and opinions regarding the above matter as shown below.

Summary of professional qualifications.

I received a B.S. degree in Chemistry from the University of Illinois in 1969, and M.S.P.H. (1973) and Ph.D. (1974) degrees in Environmental Sciences and Engineering from the University of North Carolina. My Ph.D. dissertation involved characterization of exposures to airborne chemicals in the rubber industry. In 1974, I became a staff member at the Los Alamos Scientific Laboratory where I developed air monitoring methods for several carcinogenic substances. I then joined the faculty of the School of Public Health at the University of California, Berkeley, in 1976, as an Assistant Professor of Occupational Health. At Berkeley, I developed a teaching program in industrial hygiene and continued my research on the assessment of airborne chemical exposures. I was promoted to Associate Professor (with tenure) in 1982 and to Full Professor in 1989. In 1990, I left Berkeley to become Full Professor at the School of Public Health of the University of North Carolina. There, I continued my work on

assessment of chemical exposures, based upon both environmental measurements and biomarkers of exposure. In 2006, I returned to the University of California, Berkeley, where I am now Professor of Environmental Health in the School of Public Health.

Throughout my career, I have received extramural funding for my research from both public and private sources. Public sources of funding include the National Institutes of Health, the National Institute for Occupational Safety and Health of the Centers for Disease Control, and the U.S. Air Force. Private funding sources include the American Petroleum Institute, the Nickel Producers Environmental Research Association, the American Chemistry Council and the Center to Protect Workers Rights.

I am internationally recognized for my work in quantitation of chemical exposures using air and biological measurements, using protein adducts to measure in vivo doses of reactive chemicals and using biomarkers to explore toxicokinetic relationships in humans and animals. More recently, I have been recognized as a leading proponent of the ‘exposome’ concept for characterizing all exposures that contribute to human diseases including those derived from the diet and endogenous processes. Since 1976, I have published 213 research papers in peer-reviewed journals, as well as 15 books or book chapters and 18 letters, editorials and workshop summaries.

Since 1990 I have been invited to present 212 scientific papers or lectures at world-wide venues in the fields of exposure assessment, toxicology, epidemiology and statistics. I have taught graduate courses on quantitative exposure assessment at the Universities of California and North Carolina, including courses entitled “Advanced Methods of Exposure Assessment,” “Quantitative Exposure Assessment” and “Exposure Assessment and Control”. I have also

taught short courses on topics related to chemical exposure assessment and the exposome throughout the U.S. as well as in the U.K., the Netherlands, France, Italy, Brazil and China.

During my career I have received awards for contributions to the field of exposure assessment and other areas of science including: Distinguished Lecturer in the Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD (2008), the Jerome J. Wesolowski Award for sustained and outstanding contributions to the knowledge and practice of human exposure assessment, International Society of Exposure Science (2010), the Friend E. Clark Lecturer, awarded annually to a chemist with an outstanding record of academic achievement, Department of Chemistry, West Virginia University (2012) and the Centennial Whittenberger Lecturer, Department of Environmental Health, Harvard School of Public Health, Boston, MA (2013).

I have held honorary appointments at several universities and research institutes, including the London School of Hygiene and Tropical Medicine, University of London, UK (1983-1984), the INSERM Environmental and Occupational Epidemiology Unit, Paris, France (1995), the Institute for Occupational Medicine, Edinburgh, Scotland (2000-2001), the Institute for Risk Assessment Science, Utrecht University, the Netherlands (2001), the Institute for Occupational Health (AMI), Copenhagen, Denmark (2001), the Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD (2003), Department of Epidemiology and Biostatistics, Imperial College, London (2012) and the International Agency for Research on Cancer, Lyon, France (2013). I have served on national and international committees including the Committee on Environmental Health Implications of Emerging Technologies, National Academy of Sciences (2008-2013), Environmental Health Committee, Science Advisory Board, U.S. Environmental Protection

Agency (1984–1991), the Safety and Occupational Health Study Section of the National Institute for Occupational Safety and Health (1985-1989) and the Environmental Health Committee of the International Council on Metals and the Environment (2001–2002).

Opinions regarding CERT v. Starbucks et al.

Abbreviations: AA, acrylamide; GA, glycidamide; Hb-AA, hemoglobin adduct of AA; Hb-GA, hemoglobin adduct of GA

1. The major route of formation of AA in foods is from reactions between the amino acid asparagine and sugars, such as fructose or glucose, at high temperatures (Maillard reaction and other possible reactions). Cooked foods that contain high levels of asparagine and sugars, including coffee, are sources of AA in the diet . (Dybing et al., 2005, Xu et al., 2014, Andrzejewski et al., 2004, Granby and Fagt, 2004)
2. Administration of AA to male and female rats and mice in drinking water has caused cancers of various organs in both species and sexes. (Johnson et al., 1986, Friedman et al., 1995, NTP, 2102)
3. AA is metabolized to GA, which modifies DNA, causes mutations and is carcinogenic in rats and mice. If AA exerts its carcinogenicity through a genotoxic mode of action, then GA is likely to be the ultimate carcinogen. (Doerge et al., 2005a, Abramsson-Zetterberg, 2003, Zeiger et al., 2009, Tareke et al., 2006, Von Tungeln et al., 2012, NTP, 2013)
4. Following oral dosing of AA in rats and mice, substantial fractions of the AA and GA doses are distributed to tissues and eliminated as AA and GA and their metabolites. This indicates that AA is readily absorbed from oral dosing in rats and mice and is metabolized to GA, and that both AA and GA are efficiently distributed to tissues via the systemic circulation. The percentage of AA metabolized to GA increased with

decreasing AA doses in rats and mice (Doerge et al., 2005c, Doerge et al., 2005b, Doerge et al., 2007)

5. AA and GA are electrophiles that bind to proteins, including Hb, to form adducts in the blood. These Hb adducts can be used as dosimeters of exposure and biomarkers of internal dose for AA and GA. Controlled human exposures to AA via direct administration of AA in water and ingestion of AA-rich foods have resulted in increased concentrations of Hb-AA and Hb-GA, thereby confirming that AA is absorbed, distributed and metabolized to GA in humans. These studies indicate that human metabolism of AA to GA is not saturated at administered doses up to 3 mg AA/kg body weight, that about 1/4th of the systemic dose of AA is metabolized to GA in humans and that the systemic doses of AA and GA are about 5 times and 2 times greater, respectively, in humans than in rats at a given administered dose of AA. (Fennell et al., 2005, Vikstrom et al., 2011)
6. Given rapid uptake and distribution of AA and apparent first-order metabolism of AA to GA in humans at administered doses up to 3 mg/kg body weight, all toxicokinetic processes should be linear. This is consistent with a low-dose linear model for carcinogenicity, based upon a genotoxic mode of action where GA is the ultimate carcinogen arising from metabolism of AA. To evaluate this conjecture, I applied a simple linear model to data from two published studies that reported mutation frequencies of mouse micronuclei at increasing doses of AA, administered in drinking water up to a maximum of 30 mg AA/kg body weight/day (Abramsson-Zetterberg, 2003, Zeiger et al., 2009). The linear model provided an excellent fit to the data in each study,

and adding a quadratic term to account for curvature (non-linearity) in the dose-response relationship did not significantly improve model fit in either case.

References

- ABRAMSSON-ZETTERBERG, L. 2003. The dose-response relationship at very low doses of acrylamide is linear in the flow cytometer-based mouse micronucleus assay. *Mutat Res*, 535, 215-22.
- ANDRZEJEWSKI, D., ROACH, J. A., GAY, M. L. & MUSSER, S. M. 2004. Analysis of coffee for the presence of acrylamide by LC-MS/MS. *J Agric Food Chem*, 52, 1996-2002.
- DOERGE, D. R., DA COSTA, G. G., MCDANIEL, L. P., CHURCHWELL, M. I., TWADDLE, N. C. & BELAND, F. A. 2005a. DNA adducts derived from administration of acrylamide and glycidamide to mice and rats. *Mutat Res*, 580, 131-41.
- DOERGE, D. R., TWADDLE, N. C., BOETTCHER, M. I., MCDANIEL, L. P. & ANGERER, J. 2007. Urinary excretion of acrylamide and metabolites in Fischer 344 rats and B6C3F(1) mice administered a single dose of acrylamide. *Toxicol Lett*, 169, 34-42.
- DOERGE, D. R., YOUNG, J. F., MCDANIEL, L. P., TWADDLE, N. C. & CHURCHWELL, M. I. 2005b. Toxicokinetics of acrylamide and glycidamide in B6C3F1 mice. *Toxicol Appl Pharmacol*, 202, 258-67.
- DOERGE, D. R., YOUNG, J. F., MCDANIEL, L. P., TWADDLE, N. C. & CHURCHWELL, M. I. 2005c. Toxicokinetics of acrylamide and glycidamide in Fischer 344 rats. *Toxicol Appl Pharmacol*, 208, 199-209.
- DYBING, E., FARMER, P. B., ANDERSEN, M., FENNELL, T. R., LALLJIE, S. P., MULLER, D. J., OLIN, S., PETERSEN, B. J., SCHLATTER, J., SCHOLZ, G., SCIMECA, J. A., SLIMANI, N., TORNQVIST, M., TUIJTELAARS, S. & VERGER, P. 2005. Human exposure and internal dose assessments of acrylamide in food. *Food Chem Toxicol*, 43, 365-410.
- FENNELL, T. R., SUMNER, S. C., SNYDER, R. W., BURGESS, J., SPICER, R., BRIDSON, W. E. & FRIEDMAN, M. A. 2005. Metabolism and hemoglobin adduct formation of acrylamide in humans. *Toxicol Sci*, 85, 447-59.
- FRIEDMAN, M. A., DULAK, L. H. & STEDHAM, M. A. 1995. A lifetime oncogenicity study in rats with acrylamide. *Fundam Appl Toxicol*, 27, 95-105.
- GRANBY, S. & FAGT, S. 2004. Analysis of acrylamide in coffee and dietary exposure to acrylamide from coffee. *Analytica Chimica Acta*, 520, 177-182.
- JOHNSON, K. A., GORZINSKI, S. J., BODNER, K. M., CAMPBELL, R. A., WOLF, C. H., FRIEDMAN, M. A. & MAST, R. W. 1986. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. *Toxicol Appl Pharmacol*, 85, 154-68.
- NTP 2013. Toxicology and Carcinogenesis Studies of Glycidamide (CAS NO. 5694-008) in F344/N Nctr Rats and B633F1/Nctr Mice (Drinking Water Study). In: NATIONAL TOXICOLOGY PROGRAM, R. T. P., NC (ed.). National Toxicology Program, Research Triangle Park, NC.
- NTP 2102. Toxicology and Carcinogenesis Studies of Acrylamide (CAS No. 79-06-1) in F344/N Rats and B6C3F1 Mice (Feed and Drinking Water Studies). In: PROGRAM, N. T. (ed.). National Toxicology Program, Research Triangle Park, NC.
- TAREKE, E., TWADDLE, N. C., MCDANIEL, L. P., CHURCHWELL, M. I., YOUNG, J. F. & DOERGE, D. R. 2006. Relationships between biomarkers of exposure and toxicokinetics in Fischer 344 rats and B6C3F1 mice administered single doses of acrylamide and glycidamide and multiple doses of acrylamide. *Toxicol Appl Pharmacol*, 217, 63-75.
- VIKSTROM, A. C., ABRAMSSON-ZETTERBERG, L., NARUSZEWICZ, M., ATHANASSIADIS, I., GRANATH, F. N. & TORNQVIST, M. A. 2011. In vivo doses of acrylamide and glycidamide in humans after intake of acrylamide-rich food. *Toxicol Sci*, 119, 41-9.

VON TUNGELN, L. S., DOERGE, D. R., GAMBOA DA COSTA, G., MATILDE MARQUES, M., WITT, W. M., KOTURBASH, I., POGRIBNY, I. P. & BELAND, F. A. 2012. Tumorigenicity of acrylamide and its metabolite glycidamide in the neonatal mouse bioassay. *Int J Cancer*, 131, 2008-15.

XU, Y., CUI, B., RAN, R., LIU, Y., CHEN, H., KAI, G. & SHI, J. 2014. Risk assessment, formation, and mitigation of dietary acrylamide: current status and future prospects. *Food Chem Toxicol*.

ZEIGER, E., RECIO, L., FENNELL, T. R., HASEMAN, J. K., SNYDER, R. W. & FRIEDMAN, M. 2009. Investigation of the low-dose response in the in vivo induction of micronuclei and adducts by acrylamide. *Toxicol Sci*, 107, 247-57.

Sincerely,

A handwritten signature in black ink, appearing to read "SM Rappaport". The signature is written in a cursive, flowing style.

S. M. Rappaport, Ph.D.

EXHIBIT “C”

S. M. RAPPAPORT, Ph.D.

Consultant in Occupational and Environmental Health

**[REDACTED], CA
U.S.A.**

Tel.: 510/260-0202

March 26, 2013

Mr. Raphael Metzger
Metzger Law Group
401 E. Ocean Blvd., Suite 800
Long Beach, CA 90802
via E-mail www.toxictorts.com

Re: CERT v. Starbucks Corporation *et al.*

Dear Mr. Metzger:

As we discussed on the telephone, I read the declaration by James A. Swenberg in support of the defendants in the above action. While recognizing that acrylamide has caused mutations in experimental animals (through action of its metabolite glycidamide), Swenberg states that “at low exposures mutations reach a threshold that cannot be distinguished from those in non-exposed cells”. Because of this so-called threshold, Swenberg argues that doses of acrylamide at or below 6 mg/kg body weight do not induce micronuclei in mice and, by extension, that human cancer risks arising from ingestion of acrylamide are much lower than those estimated from low-dose linear models. In what follows, I will show that data from the two mouse-micronuclei studies cited by Swenberg (Abramsson-Zetterberg, 2003; Zeiger *et al.*, 2009) do not support a 6 mg/kg-dose threshold and are, in fact, consistent with a low-dose linear model.

Basis of Swenberg’s opinions

In opinion No. 2, Swenberg states that:

- There is strong scientific consensus that cancer is a disease that results from multiple mutations. Mutations are heritable changes in the genetic information of a cell.
- At low exposures, mutations reach a threshold that cannot be distinguished from those in non-exposed cells. This has been demonstrated for acrylamide.

In opinion No. 4, Swenberg identifies the studies of Abramsson-Zeterberg *et al.* (2003) and Zeiger *et al.* (2009) as those that demonstrate the mutagenicity of acrylamide. Both of these studies measured micronuclei (a type of mutation) in circulating erythrocytes (red blood cells) from mice to which acrylamide had been administered and from control mice.

In opinion No. 5, Swenberg states that “... the number of micronuclei were identical in controls and in exposed animals until the dose reached 6 mg/kg acrylamide (Abramsson-Zetterberg, 2003; Zeiger *et al.*, 2009)”. That is, Swenberg explicitly defines 6 mg/kg body weight as a threshold for mutagenicity in the studies of Abramsson-Zeterberg *et al.* (2003) and Zeiger *et al.* (2009). Swenberg refers repeatedly to this 6-mg/kg threshold in his declaration (opinions Nos. 2, 5, 11, 13 and 14).

Analysis of data from Abramsson-Zeterberg *et al.* (2003) and Zeiger *et al.* (2009)

Given the basis of Swenberg's opinion, it is important to determine whether the studies of Abramsson-Zeterberg *et al.* (2003) and Zeiger *et al.* (2009) do, in fact, show evidence of nonlinear production of micronuclei, consistent with a threshold dose of 6 mg/kg body weight. It should be recognized that Swenberg's opinion runs counter to the conclusions of the authors of both of these studies. That is, on p. 220 Abramsson-Zetterberg *et al.* state that the "...the dose response was found to be linear at the lowest doses..." (up to 30 mg/kg) and on p. 252 Zeiger *et al.* state "...linear regression based on administered dose revealed that a linear model provided an excellent fit to the data, and there was no significant nonlinearity..." (up to 24 mg/kg/d).

To evaluate the shapes of the dose-response relationships for the above studies of micronucleated erythrocytes in mice, I extracted the relevant data as summarized in Tables 1 and 2. Micronuclei were scored in large numbers of erythrocytes for each dose group (about 1.5 million erythrocytes by Abramsson-Zetterberg *et al.* in 5 mice per group and about 14 million erythrocytes by Zeiger *et al.* in 10 mice per group), thereby enabling the number of micronucleated cells to be estimated with great precision.

Because the study of Zeiger *et al.* also reported the concentrations of acrylamide adducts of hemoglobin (AA-Val) as well as adducts of the reactive acrylamide metabolite, glycidamide, with both hemoglobin (GA-Val) and liver DNA (GA-Gua), I used the adduct concentrations in control mice to estimate the background level of acrylamide in the diet of the animals in the Zeiger *et al.* study. This dietary contribution of 0.0433 mg/kg/d¹ was added to the administered dose, as shown in the second column of Table 2, and the sum of administered plus dietary acrylamide was used for subsequent dose-response analyses.

The shapes of the relationships between micronucleated erythrocytes and acrylamide dose were evaluated with the following three models:

$$MN = b_0 + b_1(AD), \quad (1)$$

$$MN = b_0 + b_1(AD) + b_2(AD)^2, \quad (2)$$

$$\begin{aligned} MN &= b_0 \text{ for } AD \leq 6, \text{ and} \\ MN &= b_0 + b_1(AD-6) \text{ for } AD > 6, \end{aligned} \quad (3)$$

where MN is the number of micronuclei per 1000 erythrocytes and AD is the administered dose of acrylamide in mg/kg body weight. Model 1 is a simple linear model that depicts MN as the sum of an intercept term (b_0), representing the number of micronucleated erythrocytes in unexposed mice, and a linear term [$b_1(AD)$], representing the portion of MN due to the administered dose of acrylamide. Equation 2 is a linear-quadratic model, which includes both a linear term [$b_1(AD)$] and a quadratic term [$b_2(AD)^2$] which models deviations from linearity; that is, a positive value of the quadratic coefficient (b_2) would suggest upward curvature of the dose-response curve at higher doses, while a negative value would suggest downward curvature at higher doses. Equation 3 is Swenberg's threshold model which considers values of MN to be the same for all mice having $AD \leq 6$ mg/kg and then models MN as a linear function of AD at doses above 6 mg/kg. Models 1 - 3 were fit to the two sets of data given in Tables 1 and 2, using SAS software for Windows ver. 9.3 (SAS Institute, Cary, NC).

¹ The dietary contribution was estimated as the mean of point estimates from log-scale regressions of the concentration of each of the three adducts on the administered acrylamide dose: AA-Val = 0.0413 mg/kg/d, GA-Val = 0.0169 mg/kg/d, GA-Gua = 0.0717 mg/kg/d.

Results of dose-response modeling are summarized by the estimated parameters and statistics shown in Table 3. One measure of the goodness of fit is the coefficient of determination, R^2 , representing the proportion of the variability in the data that is accounted for by the model. We see that the simple linear Model 1 had R^2 values close to one for both applications ($R^2 = 0.9803$ for Abramsson-Zetterberg *et al.* and $R^2 = 0.9918$ for Zeiger *et al.*). Addition of a quadratic term (Model 2) only marginally increased R^2 (by 0.0021 and 0.0007 for the two data sets, respectively), indicating that no appreciable curvature of the dose-response relationships could be detected over the ranges of doses investigated. Values of R^2 were smaller for Swenberg's threshold Model 3 (0.92 - 0.95), indicating worse fits to the data than those for either Models 1 or 2. Thus, based upon values of R^2 across the models, the simple linear Model 1 provided a reasonable description of the (*MN*, *AD*) data pairs in both experimental studies, a conclusion that is reinforced by the regression plots shown in Figures 1 and 2.

Another measure of model fit - that can be used to select the best candidate among competing models - is the Akaike Information Criterion (AIC), which is standard output in the SAS software. The model with the smallest AIC offers the best among the competing depictions of the underlying relationship (Burnham and Anderson, 2002). When numbers of observations are small, as in the current application where data from only 7 or 12 dose groups are available, it is recommended that AIC be corrected for the numbers of parameters (e.g. b_0 , b_1 and b_2) to prevent overfitting; this gives the statistic designated AICc.² As shown in Table 3, Model 1 has the lowest value of AICc among the three candidate models for either the Abramsson-Zetterberg *et al.* data or the Zeiger *et al.* data, and thus provides a better depiction of the true relationship between *MN* and *AD* in each case. To gauge how much better Model 1 fits the data than either Model 2 or Model 3, it is necessary to inspect the differences between the respective AICc values (designated ΔAICc), which are also shown in Table 3. Since Model 1 has the smallest AICc in both comparisons, its value of ΔAICc is zero (by definition). Models 2 and 3 have values of ΔAICc between 2.642 and 27.360. To judge the corresponding weights of evidence favoring Model 1 vs. either Model 2

or 3, I calculated the Akaike weights defined as
$$\left(w_1 = \frac{1}{1 + \exp\left(\frac{1}{2}\Delta\text{AICc}\right)} \right) \text{ and } \left(w_{(2 \text{ or } 3)} = \frac{\exp\left(-\frac{1}{2}\Delta\text{AICc}\right)}{1 + \exp\left(\frac{1}{2}\Delta\text{AICc}\right)} \right)$$

(Burnham and Anderson, 2002). As ΔAIC gets large, w_1 approaches one and $w_{(2 \text{ or } 3)}$ approaches zero.

The ratio of the two Akaike weights, i.e. $\frac{w_{\text{better}}}{w_{\text{worse}}}$, is termed the evidence ratio (E.R.) and represents the relative likelihood favoring the better model (Model 1 in this application) (Burnham and Anderson, 2002).

Now, returning to the comparisons of Models 1 and 2 for the Abramsson-Zetterberg *et al.* data (Table 3), $\Delta\text{AICc} = 6.197$ and the corresponding Akaike weights are $w_1 = 0.9568$ and $w_2 = 0.0432$, respectively, giving an E.R. of $0.9568/0.0432 = 22.2$. Thus, after fitting both models to the Abramsson-Zetterberg *et al.* data, the evidence favoring simple linear Model 1 over linear-quadratic Model 2 is extremely strong (a 22-fold greater likelihood for Model 1). From analyses of model fits to the Zeiger *et al.* data (Table 3), $\Delta\text{AICc} = 2.642$, $w_1 = 0.7894$ and $w_2 = 0.2106$, giving an E.R. of 3.75. This result points to a substantially better fit of the simple linear Model 1 than the linear-quadratic Model 2 (about a 4-fold greater likelihood).

Finally, we compare the fits of linear Model 1 vs. Swenberg's threshold Model 3, which is depicted in Figures 3 and 4 for the two data sets. The visual fits of Model 3 to both data sets are poor, with substantial overestimation of *MN* values at low acrylamide doses and underestimation of *MN* values at intermediate acrylamide doses. This lack of fit is partially reflected by the reduced values of R^2 for

² $\text{AICc} = \text{AIC} + 2k(k+1)/(n-k-1)$, where k is the number of model parameters and n is the number of observations.

Model 3 compared to those of Model 1 (Table 3) as noted above. However, the values of ΔAICc and the associated statistics provide a more compelling picture of the disparity in model fits. Indeed, ΔAICc and its associated Akaike weights indicate that the simple linear Model 1 provides a vastly better fit to each data set than does the threshold Model 3 (Abramsson-Zetterberg *et al.* data: $\Delta\text{AICc} = 7.078$, $w_1 = 0.9718$ and $w_3 = 0.0282$, giving an E.R. of 34.4; Zeiger *et al.* data: $\Delta\text{AICc} = 27.360$, $w_1 = 1.00000$ and $w_3 = 1.14\text{E-}06$, giving an E.R. of 873,182). Thus the likelihood favoring the linear model is 34-fold to 873,000-fold greater than that for Swenberg's threshold model.

Conclusion

Swenberg based his opinion of a threshold dose for mutagenicity of acrylamide on studies of micronucleated erythrocytes in mice by Abramsson-Zetterberg *et al.* (2003) and Zeiger *et al.* (2009). Yet, my analyses of the published data from these studies do not support Swenberg's opinion that acrylamide is only mutagenic at administered doses above 6 mg/kg body weight (Figures 3 and 4). Indeed, my results support the conclusions of the original authors that a linear model adequately describes the relationship between mutagenicity - as indicated by micronucleated erythrocytes in mice - and the administered dose of acrylamide (Abramsson-Zetterberg, 2003; Zeiger *et al.*, 2009). Since many carcinogens are also mutagens, the apparent *linear* relationships between mutations and administered dose, shown in Figures 1 and 2, support the default assumption of a low-dose linear relationship between cancer risk and acrylamide dose that underlies the State of California's action under Proposition 65.

I would be happy to discuss these analyses and to provide additional details if needed.

Sincerely,



Stephen M. Rappaport, Ph.D.

Table 1. Data from Abramsson-Zeterberg *et al.* (2003) showing numbers of micronucleated erythrocytes (MN) in mice (5 mice per dose group). Acrylamide was administered with a single i.p. injection.

Admin. dose (mg/kg)	No. cells analyzed	No. MN	No. MN per 1000 cells
0	1,500,302	1,781	1.1871
1	1,621,864	1,973	1.2165
3	1,563,471	1,894	1.2114
6	1,654,353	2,297	1.3885
12	1,595,098	2,255	1.4137
24	1,572,732	2,724	1.7320
30	1,488,395	2,844	1.9108

Table 2. Data from Zeiger *et al.* (2009)(2003) showing numbers of micronucleated erythrocytes (MN) in mice (10 mice per dose group). Acrylamide was administered by gastric intubation daily for 28 days.

Admin. dose (mg/kg/d)	Dose + diet (mg/kg/d)*	No. cells analyzed	No. MN	No. MN per 1000 cells
0	0.0433	13,416,986	18,724	1.3955
0.125	0.1683	13,645,534	20,228	1.4824
0.25	0.2933	13,234,542	19,074	1.4412
0.5	0.5433	14,900,270	21,493	1.4425
1	1.0433	13,747,928	20,175	1.4675
2	2.0433	14,199,974	20,954	1.4756
4	4.0433	13,350,036	20,608	1.5437
6	6.0433	13,939,292	22,696	1.6282
8	8.0433	13,742,735	22,898	1.6662
12	12.0433	12,709,454	22,523	1.7721
16	16.0433	12,609,757	24,115	1.9124
24	24.0433	11,625,955	25,248	2.1717

* Includes a dietary contribution of 0.0433 mg/kg/d that was estimated in the current analysis from levels of hemoglobin and DNA adducts reported in the same animals.

Table 3. Results of regression models of mutagenicity data from studies of micronucleated erythrocytes in mice exposed to acrylamide. In each model the dependent variable is the number of micronuclei per 1000 erythrocytes (*MN*) and the dependent variable is the administered dose of acrylamide in mg/kg body weight [*AD*]. The number of dose groups (including controls) was 7 in the study of Abramsson- Zetterberg *et al.* (2003) and 12 in the study of Zeiger *et al.* (2009).

Dataset	Model	\hat{b}_0	\hat{b}_1	\hat{b}_2	R^2	AIC	AICc	Model 1 vs. 2			Model 1 vs. 3		
								$\Delta AICc$	w	E.R.	$\Delta AICc$	w	E.R.
Abramsson- Zetterberg <i>et al.</i> (2003)	1	1.18128	0.02357		0.9803	-42.2852	-39.285	0	0.9568	22.2	0	0.9718	34.4
	2	1.19400	0.01895	0.000157	0.9824	-41.0878	-33.088	6.197	0.0432				
	3	1.25031	0.02725		0.9457	-41.0376	-32.208				7.078	0.0282	
Zeiger <i>et al.</i> (2009)	1	1.42826	0.03038		0.9918	-89.6694	-88.336	0	0.7894	3.75	0	1.00000	873,182
	2	1.43284	0.02797	0.000113	0.9925	-88.6937	-85.694	2.642	0.2106				
	3	1.49826	0.03921		0.9201	-62.3096	-60.976				27.360	1.14E-06	

Legend: Models as defined in the text: Model 1 is the linear model of numbers of micronuclei vs. the administered dose of acrylamide (mg/kg body weight); Model 2 is the linear-quadratic model; Model 3 is Swenberg's threshold model with a threshold dose of 6 mg/kg; model parameters (as defined in the text): \hat{b}_0 is the estimated intercept, \hat{b}_1 is the estimated coefficient for the linear term (*AD*) and \hat{b}_2 is the estimated the coefficient for the quadratic term [$(AD)^2$]; R^2 is the coefficient of determination; AIC is the Akaike information criterion; AICc is AIC corrected for numbers of model parameters; $\Delta AICc$ is the difference in AICc between Model 1 and either Model 2 or 3; w is the Akaike weight showing the likelihood that the indicated model provides a better description of underlying relationship; E.R. is the evidence ratio given as the ratio of Akaike weights (better model/worse model).

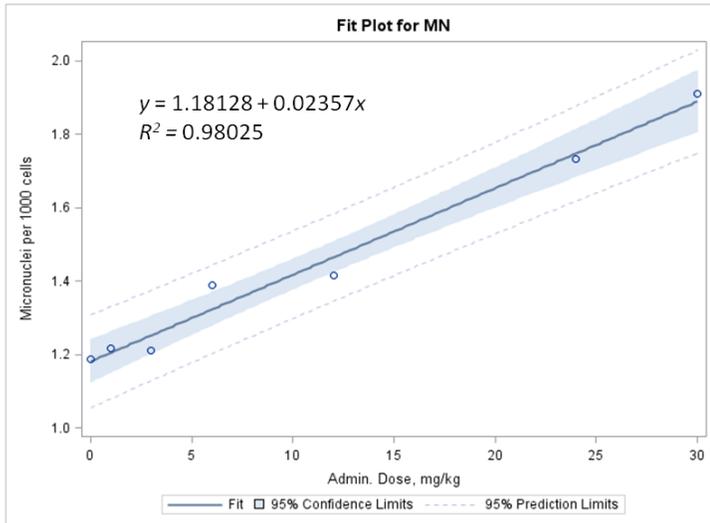


Figure 1. Dose-response relationship from simple linear regression (Model 1) of micronucleated erythrocytes on the administered acrylamide dose (data from Abramsson-Zeterberg *et al.* (2003) as shown in Table 1).

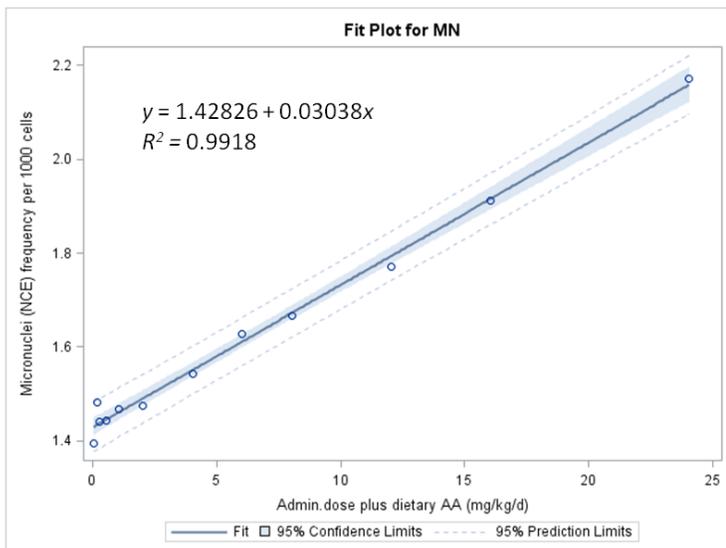


Figure 2. Dose-response relationship from simple linear regression (Model 1) of micronucleated erythrocytes on the administered acrylamide dose (data from Zeiger *et al.* (2009), as shown in Table 2).

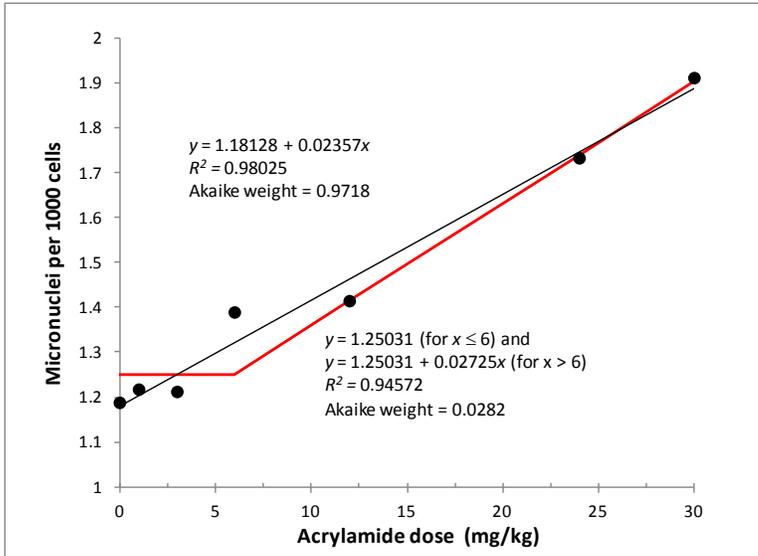


Figure 3. Dose-response relationship between micronucleated erythrocytes and the administered acrylamide dose, based upon data from Abramsson-Zeterberg *et al.* (2003). The linear model (top) is the same as shown in Figure 1. The threshold model (bottom) assumes that numbers of micronucleated erythrocytes cannot be distinguished from control values at or below an acrylamide dose of 6 mg/kg. The Akaike weight indicates the likelihood that the particular model provides a better description of the data.

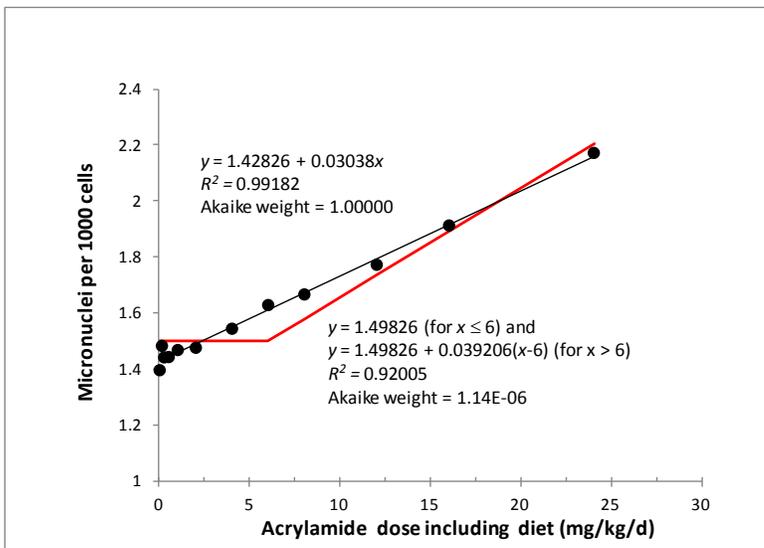


Figure 4. Dose-response relationship between micronucleated erythrocytes and the administered acrylamide dose, based upon data from Zeiger *et al.* (2009). The linear model (top) is the same as shown in Figure 2. The threshold model (bottom) assumes that numbers of micronucleated erythrocytes cannot be distinguished from control values at or below an acrylamide dose of 6 mg/kg. The Akaike weight indicates the likelihood that the particular model provides a better description of the data.

EXHIBIT “D”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT NO. 323

HON. ELIHU M. BERLE, JUDGE

COUNCIL FOR EDUCATION AND)
RESEARCH ON TOXICS,)

PLAINTIFF,)

VS.)

NO. BC435759

STARBUCKS CORPORATION,)
ET AL.,)

DEFENDANTS.)

AND CONSOLIDATED ACTION.)

REPORTER'S TRANSCRIPT OF TRIAL PROCEEDINGS

TUESDAY, SEPTEMBER 30, 2014

MORNING SESSION

APPEARANCES:

FOR THE PLAINTIFF:

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CCROLA JOB
NO. 114593

DANA L. SHELLEY, RPR, CSR #10177
OFFICIAL REPORTER PRO TEM

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(NONE.)

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1 CASE NUMBER: BC435759
2 CASE NAME: CERT VS. STARBUCKS
3 DEPARTMENT: 323 HON. ELIHU M. BERLE
4 REPORTER: DANA SHELLEY, RPR, CSR #10177
5 LOS ANGELES, CALIFORNIA TUESDAY, SEPTEMBER 30, 2014
6 TIME: 9:11 A.M.
7 APPEARANCES: (AS HERETOFORE NOTED.)
8

9 THE COURT: BACK ON THE RECORD IN THE CASE OF CERT
10 VS. STARBUCKS.

11 COUNSEL, READY TO PROCEED?

12 MR. HOLDREN: YES, YOUR HONOR.

13 THE COURT: I DO HAVE ONE MATTER I WANTED BRING TO
14 COUNSEL'S ATTENTION.

15 I'M A LITTLE CONCERNED ABOUT THE SCHEDULING
16 WITH REGARD TO OCTOBER 10TH BECAUSE -- I'M LOOKING AT --
17 OCTOBER 8TH, RATHER. DR. MELNICK IS GOING TO START
18 TESTIFYING ON THE 6TH, AND THE DEPOSITION IS SCHEDULED
19 FOR 6TH TOO. AND THE INTENTION WAS TO CONCLUDE ON THE
20 8TH.

21 I'M A LITTLE CONCERNED ABOUT THE SCHEDULING.
22 I TOLD YOU I HAD TO RECESS EARLIER, AND IT MIGHT BE
23 EARLIER THAN 3:00 O'CLOCK. IT MAY BE -- I'VE SCHEDULED
24 SOME MATTERS IN THE AFTERNOON. WE MAY HAVE TO RECESS AT
25 12:00.

26 I DON'T WANT TO HAVE A PROBLEM WITH DR.
27 MELNICK STILL ON THE STAND AND COUNSEL TELLING ME THEY
28 HAVEN'T COMPLETED THE EXAMINATION. I'M JUST THINKING

1 MAYBE WE SHOULD REVERSE THE WEEKS AND HAVE DR. MELNICK
2 COME ON THE 14TH.

3 MR. METZGER: YOUR HONOR, I BELIEVE THAT WEEK
4 THERE'S ONLY TWO DAYS, BECAUSE MONDAY IS A HOLIDAY AND
5 YOU'RE DARK ON THE 16TH AND 17TH.

6 THE COURT: WELL, MAYBE WE'LL HAVE TO CHANGE THAT,
7 BECAUSE I WON'T BE HERE ON THE 16TH. MAYBE WE'LL CHANGE
8 THAT ON THE 17TH. OR THE WAY THINGS ARE GOING, WE MAY
9 GO INTO THE FOLLOWING WEEK.

10 MR. METZGER: I THINK THAT COULD WORK.

11 THE COURT: ALL RIGHT. SO WE DON'T HAVE TO DECIDE
12 THAT NOW.

13 MR. METZGER: YES.

14 THE COURT: BUT I SUGGEST THE PARTIES MEET AND
15 CONFER TO RESCHEDULE DR. MELNICK. WE DON'T WANT -- AND
16 MAYBE THAT WILL GIVE YOU MORE TIME TO TAKE HIS
17 DEPOSITION.

18 IN FACT, IT MAY VERY WELL BE -- THAT'S UP TO
19 YOU -- THAT YOU TAKE HIS DEPOSITION ON THE 13TH AND THEN
20 HAVE HIM TESTIFY THE 14TH, 15TH, AND 17TH. SO THINK
21 ABOUT THAT.

22 OTHERWISE, THE FOLLOWING WEEK ON THE 19TH,
23 20TH, AND 21ST. I DON'T WANT TO GO DOWN TO -- TAKE A
24 RISK OF OCTOBER 8TH, AND COUNSEL ARE TELLING ME, "GEE, I
25 HAVEN'T FINISHED EXAMINING HIM," AND HE HAS TO COME BACK
26 FOR A SECOND SESSION.

27 MR. METZGER: I APPRECIATE THAT, YOUR HONOR.

28 WHAT I DON'T KNOW AT THIS POINT IS IF I CAN

1 HAVE ANOTHER WITNESS HERE ON THE 6TH. I'LL HAVE TO TRY
2 TO WORK THAT OUT.

3 THE COURT: WELL, IT WOULD WORK. IF WE COULD
4 SCHEDULE IT FOR THE WEEK OF THE 20TH, THAT WORKS TOO.
5 SO WHY DON'T YOU TALK TO COUNSEL AND SEE IF YOU CAN WORK
6 OUT SOMETHING.

7 MR. METZGER: THANK YOU, YOUR HONOR.

8 THE COURT: ALL RIGHT. SO YOU'RE GOING TO CALL
9 THE NEXT WITNESS.

10 MR. METZGER: YES, YOUR HONOR. THE PLAINTIFFS
11 WOULD CALL AS THEIR FIRST WITNESS DR. STEPHEN --
12 PROFESSOR STEPHEN RAPPAPORT.

13 THE COURT: OKAY.

14 THE CLERK: SIR, WILL YOU PLEASE RAISE YOUR RIGHT
15 HAND TO BE SWORN.

16
17 STEPHEN M. RAPPAPORT,
18 CALLED AS A WITNESS BY THE PLAINTIFF, WAS SWORN AND
19 TESTIFIED AS FOLLOWS:

20 THE CLERK: THANK YOU. PLEASE BE SEATED.

21 AND WILL YOU STATE AND SPELL YOUR NAME FOR
22 THE RECORD.

23 THE WITNESS: MY NAME IS STEPHEN M. RAPPAPORT.
24 THAT'S S-T-E-P-H-E-N R-A-P-P-A-P-O-R-T.

25 THE CLERK: THANK YOU.

26 THE COURT: GOOD MORNING, MR. RAPPAPORT. WILL YOU
27 PLEASE PULL THE MICROPHONE A LITTLE CLOSER TO YOU.

28 AND MR. METZGER, PLEASE PROCEED.

1 MR. METZGER: THANK YOU.

2

3

DIRECT EXAMINATION

4 BY MR. METZGER:

5 Q YOU ARE A PROFESSOR, ARE YOU NOT?

6 A YES, I AM.

7 Q AND ALSO A PH.D.?

8 A YES.

9 Q ALL RIGHT. I WILL EITHER CALL YOU
10 "PROFESSOR" OR "DOCTOR," THEN, AS WE PROCEED, IF THAT'S
11 ALL RIGHT.

12 PROFESSOR RAPPAPORT, IS THIS YOUR FIRST TIME
13 TESTIFYING AS AN EXPERT WITNESS IN COURT?

14 A YES.

15 Q ALL RIGHT. WE HAVE A FEW HOUSEKEEPING
16 MATTERS I'D LIKE TO TAKE CARE OF. FIRST, I'D LIKE TO
17 SHOW YOU A DOCUMENT THAT HAS BEEN MARKED AS EXHIBIT 287
18 AND ASK YOU IF THIS IS YOUR CURRICULUM VITAE.

19 A YES.

20 (EXHIBIT 287 MARKED FOR IDENTIFICATION.)

21 Q BY MR. METZGER: AND DOES IT SUMMARIZE YOUR
22 ACADEMIC AND PROFESSIONAL ACCOMPLISHMENTS?

23 A YES, THROUGH APRIL 14TH OF THIS YEAR.

24 Q DOES IT INCLUDE A LIST OF YOUR PEER-REVIEWED
25 PUBLICATIONS?

26 A YES, ASIDE FROM A FEW THAT WERE PUBLISHED
27 SINCE APRIL.

28 Q IS THE INFORMATION ON EXHIBIT 287 ACCURATE?

1 A YES.

2 MR. METZGER: YOUR HONOR, I WOULD OFFER IN
3 EVIDENCE EXHIBIT 287.

4 THE COURT: ANY OBJECTION?

5 MR. SCHURZ: NO OBJECTION, YOUR HONOR.

6 THE COURT: ALL RIGHT. 287 IS IN EVIDENCE.

7 (EXHIBIT 287 RECEIVED IN EVIDENCE.)

8 Q BY MR. METZGER: DR. RAPPAPORT, HAVE YOU
9 PREPARED SOME WRITTEN REPORTS FOR THIS CASE?

10 A YES.

11 Q I WILL SHOW YOU A LETTER THAT HAS A
12 TYPEWRITTEN DATE OF MARCH 26, 2013, WHICH IS CROSSED OUT
13 WITH A -- AND HAS A HANDWRITTEN DATE, INSTEAD OF THAT,
14 OF APRIL 14, 2014.

15 THIS IS EXHIBIT 315, IS IT NOT?

16 A YES.

17 (EXHIBIT 315 MARKED FOR IDENTIFICATION.)

18 Q BY MR. METZGER: AND IS THIS A REPORT THAT
19 YOU PREPARED FOR THIS CASE?

20 A YES.

21 Q ALL RIGHT. NOW I'D LIKE TO SHOW YOU A
22 LETTER THAT'S DATED MARCH 26, 2013, WHICH HAS BEEN
23 MARKED AS EXHIBIT 16 -- 316; EXCUSE ME.

24 IS EXHIBIT 316 ANOTHER REPORT THAT YOU
25 PREPARED REGARDING THIS CASE?

26 A YES.

27 (EXHIBIT 316 MARKED FOR IDENTIFICATION.)

28 Q BY MR. METZGER: NOW I'D LIKE TO SHOW YOU --

1 MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT TO --

2 THE COURT: THERE'S NOTHING TO OBJECT TO. HE'S
3 JUST SHOWING HIM A PIECE OF PAPER. NOTHING HAS BEEN
4 OFFERED FOR ANYTHING.

5 MR. SCHURZ: THANK YOU.

6 Q BY MR. METZGER: NOW I'M SHOWING YOU A
7 LETTER DATED APRIL 20, 2014, THAT HAS BEEN MARKED AS
8 EXHIBIT 317. IS THIS LETTER YET ANOTHER REPORT THAT YOU
9 PREPARED REGARDING THIS CASE?

10 A YES.

11 (EXHIBIT 317 MARKED FOR IDENTIFICATION.)

12 Q BY MR. METZGER: DR. RAPPAPORT, NOW I'M
13 SHOWING YOU A TWO-PAGE DOCUMENT THAT APPEARS TO BE A
14 COMPUTER PRINTOUT, THAT HAS BEEN MARKED AS EXHIBIT 298.

15 CAN YOU TELL US VERY BRIEFLY WHAT THIS IS.

16 A THIS REPRESENTS CALCULATIONS THAT I
17 PERFORMED, USING A COMPUTER PROGRAM, TO DETERMINE THE
18 NUMBER -- NUMBERS OF CUPS OF COFFEE PER DAY CONSUMED BY
19 A SAMPLE OF AMERICANS.

20 (EXHIBIT 298 MARKED FOR IDENTIFICATION.)

21 Q BY MR. METZGER: AND DID YOU PREPARE THAT
22 FOR THIS CASE?

23 A I DID.

24 Q WE HAVE A FEW MORE, I THINK.

25 NOW I'M SHOWING YOU A SINGLE-PAGE DOCUMENT
26 WHICH HAS BEEN MARKED AS EXHIBIT 299. WOULD YOU BRIEFLY
27 TELL US WHAT THIS IS.

28 A THESE ARE ALSO CALCULATIONS THAT I

1 PERFORMED, AT YOUR REQUEST, REGARDING THE DOSE-RESPONSE
2 RELATIONSHIP FOR ACRYLAMIDE LEADING TO THYROID CANCERS
3 IN EXPERIMENTAL ANIMALS.

4 (EXHIBIT 299 MARKED FOR IDENTIFICATION.)

5 Q BY MR. METZGER: THANK YOU.

6 A AND THESE WERE BASED ON DATA THAT HAVE BEEN
7 PROVIDED BY DR. DOURSON, I THINK, WHO IS A CONSULTANT
8 FOR THE OTHER SIDE.

9 Q ALL RIGHT. LET'S SEE. I WANT TO SHOW YOU
10 ALSO ANOTHER LETTER. THIS IS EXHIBIT 318. IT'S A
11 LETTER DATED AUGUST 16, 2007.

12 THE COURT: WHAT IS THE NUMBER ON THAT DOCUMENT?

13 MR. METZGER: I'M SORRY. IT'S EXHIBIT 318.

14 THE COURT: 318.

15 (EXHIBIT 318 MARKED FOR IDENTIFICATION.)

16 Q BY MR. METZGER: DOES THIS LETTER SET FORTH
17 OPINIONS THAT YOU PREPARED REGARDING THE TOXICOKINETICS
18 OF ACRYLAMIDE FOR THE PRIOR ACRYLAMIDE LITIGATION
19 REGARDING FRENCH FRIES?

20 MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT TO ANY
21 QUESTIONS RELATING TO 318. IT'S IRRELEVANT AND OUTSIDE
22 THE SCOPE. THIS WITNESS SPECIFICALLY TESTIFIED --

23 THE COURT: OBJECTION OVERRULED.

24 MR. METZGER: DID WE GET AN ANSWER?

25 THE WITNESS: YES, IT IS A REPORT I PREPARED.

26 Q BY MR. METZGER: THANK YOU.

27 NOW, HAVE YOU UPDATED THE OPINIONS THAT
28 APPEAR IN EXHIBIT 318 FOR THIS CASE?

1 MR. SCHURZ: YOUR HONOR, WE'D OBJECT TO 318. THIS
2 WITNESS TESTIFIED --

3 THE COURT: NOTHING HAS BEEN OFFERED YET.
4 OBJECTION OVERRULED.

5 THE WITNESS: YES, I DID UPDATE MY OPINIONS.

6 Q BY MR. METZGER: AND ARE THE UPDATED
7 OPINIONS REGARDING THE TOXICOKINETICS OF ACRYLAMIDE
8 CONTAINED IN EXHIBIT 315, WHICH YOU'VE ALREADY
9 IDENTIFIED?

10 A YES.

11 Q FOR PURPOSES OF YOUR OPINIONS IN THIS CASE
12 REGARDING THE TOXICOKINETICS OF ACRYLAMIDE, WILL YOU BE
13 RELYING ON YOUR UPDATED OPINIONS, EXHIBIT 315, RATHER
14 THAN THE OPINIONS FROM 2007, WHICH WERE -- ARE EXHIBIT
15 318?

16 A I WILL.

17 Q WHY DON'T YOU PUT THAT REPORT ASIDE BECAUSE
18 IT'S A SUPERSEDED REPORT, THE 2007 ONE. THAT MAY AVOID
19 SOME OBJECTIONS.

20 NOW, DR. RAPPAPORT, IF YOU NEED TO REFER TO
21 ANY OF YOUR REPORTS IN ANSWERING ANY OF THE QUESTIONS
22 THAT I OR MR. SCHURZ ASKS YOU, WILL YOU FEEL FREE TO DO
23 SO?

24 A YES.

25 Q ALL RIGHT. NOW, DR. RAPPAPORT, AT MY
26 REQUEST, DID YOU PREPARE A POWERPOINT PRESENTATION TO
27 FACILITATE THE -- TO HELP EVERYONE UNDERSTAND YOUR
28 OPINIONS IN THIS CASE?

1 A YES.

2 (PAUSE IN PROCEEDINGS.)

3 Q BY MR. METZGER: SHOWING YOU WHAT HAS BEEN
4 MARKED AS EXHIBIT 290, IS EXHIBIT 290 THE POWERPOINT
5 PRESENTATION THAT YOU PREPARED?

6 A YES.

7 (EXHIBIT 290 MARKED FOR IDENTIFICATION.)

8 Q BY MR. METZGER: NOW, IS THE INFORMATION
9 THAT'S CONTAINED IN THE POWERPOINT PRESENTATION -- IS
10 ALL OF THAT INFORMATION THAT WAS CONTAINED EITHER IN
11 YOUR CURRICULUM VITAE OR THE REPORTS THAT YOU HAVE
12 PREPARED FOR THIS CASE?

13 A YES.

14 Q ALL RIGHT. LET'S TALK A LITTLE ABOUT YOU,
15 IF WE CAN. FIRST, WILL YOU BRIEFLY TELL THE COURT ABOUT
16 YOUR EDUCATIONAL BACKGROUND.

17 A I OBTAINED A BACHELOR'S DEGREE IN CHEMISTRY
18 FROM THE UNIVERSITY OF ILLINOIS IN 1965. I THEN WENT TO
19 GRADUATE SCHOOL AT THE UNIVERSITY OF NORTH CAROLINA,
20 RECEIVED A MASTER'S DEGREE AND A PH.D. IN 1973.

21 Q IN WHAT SUBJECTS?

22 A ENVIRONMENTAL SCIENCES AND ENGINEERING.

23 Q ENVIRONMENTAL SCIENCE AND ENGINEERING?

24 A SCIENCES AND ENGINEERING.

25 Q THANK YOU.

26 A YES.

27 Q ALL RIGHT. NOW, I'D LIKE TO DISCUSS, IF WE
28 COULD, YOUR SPECIFIC SCIENTIFIC RESEARCH INTERESTS. AND

1 I SEE THAT THEY WERE LISTED ON YOUR CURRICULUM VITAE.
2 AND THEY'VE BEEN BULLET-POINTED IN THE POWERPOINT.

3 DO YOU SEE THAT?

4 A YES.

5 Q OKAY. SO THE FIRST ONE THAT YOU LISTED ON
6 YOUR CURRICULUM VITAE IS "PROFILING BIOMARKERS IN
7 STUDIES OF HUMAN EXPOSURE." IS THAT A RESEARCH INTEREST
8 OF YOURS?

9 A YES, IT IS.

10 Q WOULD YOU EXPLAIN TO THE COURT WHAT
11 BIOMARKERS ARE.

12 A YES. BIOMARKERS ARE ENTITIES THAT CAN BE
13 MEASURED IN LIVING SYSTEMS. IN MY CASE, I'M INTERESTED
14 IN HUMAN BEINGS. AND THEY REPRESENT MEASURES OF
15 EXPOSURE OR DAMAGE THAT'S CAUSED BY THESE EXPOSURES.

16 IT COULD BE A CHEMICAL THAT'S INHALED OR
17 INGESTED, OR A PRODUCT OF THAT CHEMICAL'S METABOLISM, OR
18 A PRODUCT OF THE DAMAGE THAT THAT CHEMICAL OR ITS
19 METABOLITES CAUSE TO TISSUES IN THE BODY.

20 Q ARE THERE DIFFERENT TYPES OF BIOMARKERS,
21 GENERALLY?

22 A YES. AND THEY'RE USUALLY DISTINGUISHED OR
23 DIFFERENTIATED ACCORDING TO WHETHER THEY PRIMARILY
24 REFLECT EXPOSURES THAT HAVE BEEN RECEIVED OR DAMAGE
25 THAT'S INCURRED AS A RESULT OF THESE EXPOSURES.

26 AND THOSE ARE REFERRED TO USUALLY AS
27 "BIOMARKERS OF EFFECT," WHEREAS THE FORMER ARE REFERRED
28 TO AS BIOMARKERS OF EXPOSURE.

1 Q OKAY. HOW LONG HAS PROFILING BIOMARKERS
2 BEEN A RESEARCH AREA OF YOURS?

3 A SINCE THE MID 1980S.

4 Q AND VERY GENERALLY -- OR BRIEFLY, WOULD YOU
5 DESCRIBE YOUR EXPERIENCE AND RESEARCH REGARDING
6 PROFILING BIOMARKERS IN STUDIES OF HUMAN EXPOSURE.

7 A WE WOULD SEEK POPULATIONS OF INDIVIDUALS WHO
8 HAD PARTICULAR EXPOSURES. AND IN MOST CASES, THESE WERE
9 WORKERS WHO PERFORMED DUTIES IN FACTORIES WHERE TOXIC
10 CHEMICALS WERE USED.

11 SOME OF THE CHEMICALS THAT WE INVESTIGATED
12 WERE STYRENE, THAT'S USED IN THE MANUFACTURE OF
13 PLASTICS; BENZENE, THAT'S A CONTAMINANT OF GASOLINE; AND
14 SO FORTH.

15 WE WOULD MEASURE EXPOSURES TO THESE
16 CONTAMINANTS AND ALSO OBTAIN BIOSPECIMENS FROM THE
17 WORKERS. THE BIOSPECIMENS WERE BLOOD, IN MANY CASES;
18 SOMETIMES URINE.

19 AND WE WOULD THEN LOOK FOR BIOMARKERS IN
20 THESE SPECIMENS, AND WE COULD RELATE THE LEVELS OF THESE
21 BIOMARKERS WITH THE EXPOSURE THAT WE HAD DOCUMENTED IN
22 THE SAME SUBJECTS.

23 Q HAVE YOU PUBLISHED ARTICLES ON THIS TOPIC?

24 A YES, MANY.

25 Q HAVE YOU LECTURED ON THIS TOPIC?

26 A YES.

27 Q AND HAVE YOU TAUGHT YOUR STUDENTS ON THIS
28 TOPIC?

1 A YES.

2 Q BY THE WAY, WHERE ARE YOUR STUDENTS?

3 A WELL, MY STUDENTS ARE ALL OVER THE WORLD --
4 FORMER STUDENTS. MY CURRENT STUDENTS ARE AT THE
5 UNIVERSITY OF CALIFORNIA BERKELEY.

6 Q THE NEXT RESEARCH INTEREST LISTED ON YOUR
7 CURRICULUM VITAE IS "INVESTIGATING RELATIONSHIPS BETWEEN
8 CHEMICAL EXPOSURES AND BIOMARKER LEVELS." CAN YOU
9 EXPLAIN WHAT THAT ENTAILS.

10 A YES. IN HUMANS, IT'S DIFFICULT TO
11 INVESTIGATE THE SO-CALLED EXPOSURE-RESPONSE
12 RELATIONSHIP. IT'S BECAUSE EXPOSURES ARE DIFFICULT TO
13 MEASURE. THEY'RE HIGHLY VARIABLE WITHIN SUBJECTS. THE
14 SAME PERSON IS EXPOSED TO DIFFERENT LEVELS --

15 (INTERRUPTION IN PROCEEDINGS.)

16 THE WITNESS: THE SAME SUBJECTS ARE EXPOSED TO
17 DIFFERENT LEVELS OF CHEMICALS OR CONTAMINANTS OVER TIME.

18 AND FOR THIS REASON, WE HAVE INVESTIGATED --
19 OR WE'VE DEVELOPED METHODS AND EXPERTISE TO ALLOW US TO
20 CAREFULLY DOCUMENT THESE EXPOSURES; AND ALSO, THE
21 INTERNAL LEVELS REPRESENTED BY THE BIOMARKERS.

22 PUTTING THE TWO TOGETHER, WE CAN EXAMINE THE
23 SHAPE OF THIS EXPOSURE-RESPONSE RELATIONSHIP IN SPECIFIC
24 WAYS.

25 WE CAN LOOK FOR, FOR EXAMPLE, THE LINEARITY
26 PROCESSES -- THAT I'M SURE WE'LL BE TALKING ABOUT
27 LATER -- WHICH IS RELATED TO THE PRODUCTION OF, SAY, A
28 TOXIC METABOLITE FROM EXPOSURE TO A PARTICULAR

1 CONTAMINANT.

2 Q ALL RIGHT. YOU'VE BEEN REFERRING TO "WE."
3 AND WHO IS THE "WE" YOU'RE TALKING ABOUT?

4 A IT'S MY LABORATORY.

5 Q OKAY. WHEN YOU SAY YOUR LABORATORY, WHAT
6 LABORATORY ARE YOU REFERRING TO?

7 A I HAVE A LABORATORY AT THE UNIVERSITY OF
8 CALIFORNIA BERKELEY.

9 Q DOES IT HAVE A NAME?

10 A IT'S CALLED THE RAPPAPORT LABORATORY,
11 USUALLY.

12 Q AND WHAT IS THAT LABORATORY'S LABORATORY
13 RESEARCH?

14 A WELL, WE INVESTIGATE HUMAN EXPOSURES, AND WE
15 INVESTIGATE THESE BIOMARKER LEVELS IN DIFFERENT HUMAN
16 POPULATIONS.

17 Q THE THIRD RESEARCH INTEREST LISTED ON YOUR
18 CURRICULUM VITAE IS "STATISTICAL APPROACHES FOR
19 EVALUATING EXPOSURES." HOW LONG HAS THAT BEEN A
20 RESEARCH AREA OF YOURS?

21 A OH, FROM THE '70S. AS I MENTIONED, EXPOSURE
22 LEVELS TEND TO VARY GREATLY WITHIN INDIVIDUALS OVER TIME
23 AND ACROSS PEOPLE IN THE POPULATION BECAUSE SOME PEOPLE
24 HAVE HABITS OR WORK OR OTHER FUNCTIONS THAT PUT THEM IN
25 A RISK OF HIGHER EXPOSURE.

26 SO IN ORDER TO INVESTIGATE THE EXPOSURES AND
27 RESPONSES TO EXPOSURES, ONE HAS TO ADOPT A VARIETY OF
28 STATISTICAL TOOLS. AND I WAS ONE OF THE FIRST PEOPLE TO

1 REALLY INVESTIGATE AND UTILIZE THESE TOOLS IN STUDIES OF
2 HUMANS.

3 Q AND SOME OF YOUR TESTIMONY TODAY IS GOING TO
4 INVOLVE STATISTICS, IS IT NOT?

5 A YES.

6 Q WOULD YOU TELL THE COURT GENERALLY ABOUT
7 YOUR EDUCATION IN THE FIELD OF STATISTICS.

8 A WELL, I TOOK COURSES IN STATISTICS AS PART
9 OF MY GRADUATE PROGRAM; BUT MORE IMPORTANTLY, I STUDIED
10 STATISTICS AND COLLABORATED WITH A NUMBER OF
11 DISTINGUISHED STATISTICIANS IN MY CAREER.

12 AND I EVEN WROTE A BOOK THAT'S LARGELY
13 RELATED TO APPLICATIONS OF STATISTICS TO EXPOSURE
14 ASSESSMENT, WITH A DISTINGUISHED STATISTICIAN AT THE
15 UNIVERSITY OF NORTH CAROLINA.

16 Q HAVE YOU TAUGHT THESE STATISTICAL APPROACHES
17 TO YOUR STUDENTS?

18 A I HAVE. AND I'VE ALSO TAUGHT THESE
19 STATISTICAL APPROACHES IN SHORT COURSES THAT HAVE BEEN
20 GIVEN AT DIFFERENT VENUES AROUND THE WORLD.

21 Q OKAY. THE OTHER -- THE LAST RESEARCH
22 INTEREST LISTED ON YOUR CURRICULUM VITAE WAS "DEVELOPING
23 STATE-OF-THE ART METHODS FOR MEASURING MACROMOLECULAR
24 ADDUCTS IN BIOLOGICAL SAMPLES."

25 DID I SAY THAT RIGHT?

26 A YES, YOU DID.

27 Q ALL RIGHT. LET ME ASK YOU TO DEFINE SOME
28 TERMS HERE. FIRST OF ALL, WHAT IS AN ADDUCT?

1 A AN ADDUCT IS -- IT'S CHEMICAL SHORTHAND. IT
2 MEANS ADDITION PRODUCT.

3 Q I SEE.

4 A AND IT'S SIMPLY THE PRODUCT OF A REACTION
5 BETWEEN ONE CHEMICAL AND ANOTHER.

6 IN THIS CONTEXT, THE MACROMOLECULAR PIECE IS
7 USUALLY THOUGHT OF AS A LARGE BIOLOGICAL MOLECULE. ONE
8 SUCH MOLECULE IS DNA, THAT WE KNOW HAS VERY IMPORTANT
9 FUNCTIONS. AND SOME CHEMICALS CAN REACT WITH DNA TO
10 PRODUCE ADDUCTS. SOME OF THESE ADDUCTS CAN BE HARMFUL
11 TO THE DNA AND GO ON TO PRODUCE MUTATIONS.

12 THE SAME CHEMICALS THAT REACT WITH THE DNA
13 CAN ALSO REACT WITH OTHER MACROMOLECULES IN THE BODY.
14 IN MY LABORATORY, WE USUALLY INVESTIGATE PROTEINS THAT
15 ARE PRESENT IN THE SERUM. THE MAIN PROTEIN IS SERUM
16 ALBUMIN. OTHER PEOPLE INVESTIGATE ADDUCTS WITH THE
17 BLOOD PROTEIN HEMOGLOBIN.

18 Q OKAY. AND WHY IN YOUR LABORATORY HAVE YOU
19 DONE RESEARCH AND EXPERIMENTS REGARDING ADDUCTS OF
20 PROTEINS?

21 A THESE -- WHEN CHEMICALS ENTER THE BODY, MANY
22 OF THEM ARE METABOLIZED TO TOXIC FORMS. AND THESE TOXIC
23 METABOLITES ARE REACTIVE. THEY HAVE VERY SHORT
24 LIFETIMES IN THE BODY, SO THEY CAN'T BE MEASURED VERY
25 EASILY WITH DIRECT METHODS.

26 BUT THEY PRODUCE THESE ADDUCTS WITH
27 PROTEINS, SAY, AND THOSE ADDUCTS CAN BE MEASURED. SO
28 THEY GIVE YOU SORT OF THE FINGERPRINTS OF THE EXPOSURE

1 TO THAT TOXIC SUBSTANCE THAT WAS PRESENT IN THE BODY.

2 SO IT ALLOWS A WAY OF INVESTIGATING THE
3 DOSES OF TOXIC MATERIALS THAT ARE RECEIVED FROM
4 EXPOSURES FROM AIR, WATER, FOOD, AND THE LIKE.

5 Q WOULD THESE PROTEIN ADDUCTS BE A FORM OF
6 BIOMARKER?

7 A YES, THEY ARE. BIOMARKERS OF EXPOSURE,
8 ACTUALLY.

9 Q NOW, WHAT CONTRIBUTIONS HAVE YOU MADE TO
10 DEVELOPING STATE-OF-THE-ART METHODS FOR MEASURING
11 MACROMOLECULAR ADDUCTS IN BIOLOGICAL SAMPLES?

12 A MY LABORATORY IS ONE OF THE FEW THAT HAS
13 DEVELOPED TARGETED ASSAYS FOR THESE ADDUCTS. A TARGETED
14 ASSAY WOULD BE ONE THAT'S DEVELOPED FOR A SPECIFIC
15 CHEMICAL.

16 IN THIS CASE, OUR LABORATORY HAS LOOKED AT
17 BENZENE, STYRENE, AS I MENTIONED BEFORE; A WHOLE HOST OF
18 CHEMICALS CALL POLYCYCLIC AROMATIC HYDROCARBONS THAT ARE
19 PRESENT IN COMBUSTION PRODUCTS, AND SO ON.

20 Q ALL RIGHT. WHAT POSITION DO YOU CURRENTLY
21 HOLD -- OR POSITIONS DO YOU CURRENTLY HOLD AT UC
22 BERKELEY?

23 A I'M A PROFESSOR OF ENVIRONMENTAL HEALTH IN
24 THE SCHOOL OF PUBLIC HEALTH. I'M ALSO THE DIRECTOR OF
25 THE CENTER FOR EXPOSURE BIOLOGY, WHICH IS A
26 MULTIDISCIPLINARY CENTER INVOLVING SCIENCES FROM PUBLIC
27 HEALTH, FROM ENGINEERING, AND FROM CHEMISTRY, AT THE
28 UNIVERSITY OF CALIFORNIA BERKELEY.

1 Q ALL RIGHT. WILL YOU BRIEFLY TELL THE COURT
2 ABOUT SOME OF THE PRIOR POSITIONS THAT YOU HAVE HELD.

3 A YES. I WAS -- I'VE BEEN A PROFESSOR AT
4 BERKELEY TWICE. I INITIALLY ENTERED THE UNIVERSITY OF
5 CALIFORNIA AT BERKELEY IN 1976, AND I WORKED MY WAY
6 THROUGH THE PROFESSORIAL SERIES THERE TO FULL PROFESSOR.

7 THEN I LEFT IN 1990 TO GO TO BE A PROFESSOR
8 AT UNIVERSITY OF NORTH CAROLINA, WHERE I RECEIVED MY
9 PH.D. VERY SIMILAR POSITION, ALSO IN ENVIRONMENTAL
10 HEALTH.

11 THEN IN 2006, I HAD THE OPPORTUNITY TO
12 RETURN TO THE BEAUTIFUL STATE OF CALIFORNIA, IN
13 BERKELEY, AND I CAME BACK TO ASSUME WHAT WAS ESSENTIALLY
14 MY FORMER POSITION. AND I'VE BEEN THERE SINCE 2006.

15 Q ALL RIGHT. HAVE YOU ALSO HELD POSITIONS AT
16 THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND
17 HEALTH?

18 A NO. I WAS A PROGRAM DIRECTOR AT THE
19 UNIVERSITY OF NORTH CAROLINA OF A NIOSH RESEARCH CENTER,
20 OR EDUCATIONAL RESOURCE CENTER.

21 Q OKAY.

22 A AND I DID THAT FOR FIVE YEARS, WHEN I FIRST
23 WENT TO NORTH CAROLINA.

24 Q ALL RIGHT. AND HAVE YOU ALSO BEEN A PROJECT
25 DIRECTOR FOR THE NATIONAL INSTITUTE FOR ENVIRONMENTAL
26 HEALTH SCIENCES TRAINING GRANT?

27 A YES, ALSO AT NORTH CAROLINA.

28 Q OKAY. AND I ALSO SEE THAT YOU WERE CORE

1 DIRECTOR FOR EXPOSURE BIOMARKERS AND RESEARCH CORE FOR
2 THE NIEHS, THE CENTER FOR ENVIRONMENTAL HEALTH AND
3 SUSCEPTIBILITY; IS THAT CORRECT?

4 A YES. WE HAD A CENTER GRANT AT NORTH
5 CAROLINA THAT I HELPED TO BRING IN.

6 Q OKAY. HAVE YOU BEEN A VISITING SCIENTIST
7 AND RESEARCHER AT VARIOUS INSTITUTIONS IN THE UNITED
8 STATES AND EUROPE?

9 A YES, I HAVE.

10 Q I WANT TO ASK YOU ABOUT JUST A FEW OF THEM.
11 ARE YOU FAMILIAR WITH THE INSTITUTE FOR RISK ASSESSMENT
12 SCIENCE AT UTRECHT UNIVERSITY, IN THE NETHERLANDS?

13 A YES. I WAS A VISITING SCIENTIST THERE FOR
14 SIX MONTHS.

15 Q AND WOULD YOU TELL US GENERALLY WHAT YOU DID
16 THERE.

17 A YES. AT THAT TIME I WAS LOOKING -- I WAS
18 INVESTIGATING THE EXPOSURE-RESPONSE RELATIONSHIP FOR
19 STYRENE.

20 Q DID YOU TEACH STATISTICS THERE?

21 A I DID. I COLLABORATED FOR SEVERAL YEARS
22 WITH SCIENTISTS AT UTRECHT, AND WE JOINTLY TAUGHT
23 COURSES RELATED TO USE OF STATISTICS IN EXPOSURE
24 ASSESSMENT.

25 Q OKAY. AND HAVE YOU HELD ONE OR MORE
26 APPOINTMENTS AS A VISITING SCIENTIST IN THE DIVISION OF
27 CANCER, EPIDEMIOLOGY, AND GENETICS AT THE NATIONAL
28 CANCER INSTITUTE?

1 A YES. I WAS INVITED TO WORK THERE FOR A
2 SUMMER IN THE EARLY 2000S. AND DURING THAT TIME, WE
3 REVIEWED DATA THAT HAD BEEN COLLECTED IN A COLLABORATIVE
4 STUDY BETWEEN NCI SCIENTISTS AND MY LABORATORY,
5 INVOLVING BENZENE EXPOSURES IN CHINA.

6 Q HAVE YOU HELD ANY APPOINTMENTS AT THE
7 INTERNATIONAL AGENCY FOR RESEARCH ON CANCER?

8 A YES. I WAS SENIOR VISITING SCIENTIST LAST
9 YEAR, 2013, AT IARC.

10 Q AND GENERALLY, WHAT DID YOU DO AS A SENIOR
11 VISITING SCIENTIST?

12 A RECENTLY, WE'VE BEEN VERY INTERESTED IN A
13 CONCEPT CALLED THE EXPOSOME.

14 Q EXPOSOME?

15 A EXPOSOME.

16 Q E-X-P-O-S-O-M-E?

17 A YES.

18 Q OKAY. WHAT'S THAT?

19 A IT REPRESENTS EVERYTHING WE'RE EXPOSED TO
20 DURING LIFE, FROM ALL SOURCES: FROM POLLUTION, FROM
21 FOOD, FROM DRUGS, ENDOGENOUS PROCESSES. AND IT'S A
22 COMPLEMENT TO THE GENO.

23 PEOPLE ARE AWARE OF GENO AND ITS IMPLICATION
24 TO CAUSE DISEASE. WELL, MOST DISEASES ARE ACTUALLY
25 CAUSED BY EXPOSURES. WE NEED AN EXPOSOME SO WE CAN GET
26 COMPREHENSIVE INFORMATION ABOUT THE EXPOSURE.

27 THE DIRECTOR OF IARC, CHRISTOPHER WILD,
28 PROPOSED THIS CONCEPT IN 2005. AND I'VE BEEN ONE OF THE

1 FOREMOST ADVOCATES OF THIS CONCEPT, TO TRY AND DEVELOP
2 IT IN THE FIELD OF ENVIRONMENTAL HEALTH.

3 Q AND DID DR. WILD INVITE YOU TO DO WORK ON
4 THAT AT IARC?

5 A IN A SENSE. IT WAS A COMPETITIVE PROCESS.
6 SO I ACTUALLY APPLIED, AND MY APPLICATION WAS REVIEWED,
7 WITH OTHERS. AND I DID RECEIVE A FELLOWSHIP TO WORK
8 THERE.

9 Q OKAY. ARE YOU FAMILIAR WITH THE UNITED
10 STATES NATIONAL ACADEMY OF SCIENCES?

11 A YES, I AM.

12 Q HAVE YOU SERVED ON ANY COMMITTEES OF THE
13 NAS?

14 A YES. I WAS INVITED TO BE A STANDING MEMBER
15 OF A COMMITTEE WHOSE ROLE IT WAS TO INVESTIGATE RECENT
16 DEVELOPMENTS IN SCIENCE AND TECHNOLOGY AND HOW THEY HAD
17 IMPLICATIONS ON ENVIRONMENTAL HEALTH.

18 Q AND HAVE YOU PROVIDED PROFESSIONAL SERVICES
19 TO HARVARD UNIVERSITY?

20 A YES, IN A COUPLE OF CASES. IN ONE, THERE
21 WAS AN EXPERT COMMITTEE THAT WAS ORGANIZED TO REVIEW THE
22 HEALTH IMPLICATIONS OF STYRENE.

23 IN ANOTHER CASE, I WAS ASKED TO BE ON AN
24 EXTERNAL ADVISORY COMMITTEE FOR HARVARD'S CENTER FOR
25 ENVIRONMENTAL HEALTH SCIENCES. THAT'S IN THE SCHOOL OF
26 PUBLIC HEALTH.

27 AND ON ANOTHER INSTANCE, I WAS INVITED TO
28 GIVE THE WHITTENBERGER LECTURE, WHICH IS GIVEN EACH YEAR

1 AT HARVARD UNIVERSITY.

2 Q OKAY. INCIDENTALLY, HAVE YOU RECEIVED ANY
3 AWARDS FROM THE INTERNATIONAL AGENCY FOR RESEARCH ON
4 CANCER?

5 A WELL, I DID RECEIVE THE SCHOLARSHIP THAT
6 ALLOWED ME TO DO THE SABBATICAL WORK LAST YEAR.

7 Q WAS THAT A SENIOR VISITING SCIENTIST AWARD?

8 A YES, IT WAS.

9 Q ALL RIGHT. AND HAVE YOU SERVED ON
10 SCIENTIFIC ADVISORY BOARDS OF THE UNITED STATES
11 ENVIRONMENTAL PROTECTION AGENCY?

12 A YES. I WAS ON A COMMITTEE TO INVESTIGATE
13 ACUTELY TOXIC SUBSTANCES IN THE 1980S. I WAS ALSO
14 CALLED AS A CONSULTANT TO THE ENVIRONMENTAL HEALTH
15 COMMITTEE OF EPA ON A NUMBER OF OCCASIONS IN THE '80S.

16 Q ALL RIGHT. HAVE YOU RECEIVED ANY AWARDS FOR
17 YOUR PUBLICATIONS?

18 A I HAVE. THERE WERE TWO OR THREE PAPERS THAT
19 RECEIVED AWARDS FOR EITHER EXPOSURE SCIENCE OR FOR
20 TOXICOLOGY.

21 Q WAS ONE OF THEM THE JEROME WESOLOWSKI AWARD
22 FOR SUSTAINED AND OUTSTANDING CONTRIBUTIONS TO THE
23 KNOWLEDGE AND PRACTICE OF HUMAN EXPOSURE ASSESSMENT,
24 AWARDED BY THE INTERNATIONAL SOCIETY OF EXPOSURE
25 SCIENCE?

26 A WELL, THAT WAS NOT AN AWARD THAT WAS RELATED
27 SO MUCH TO ANY INDIVIDUAL PUBLICATION AS JUST TO MY
28 RECORD OF PUBLICATIONS AND WORK OVER THE YEARS.

1 Q AND DID YOU RECEIVE AN AWARD FOR A PAPER
2 THAT YOU'VE PUBLISHED ON THE EXPOSOME?

3 A YES. IT WAS THE MOST HIGHLY CITED PAPER
4 THAT WAS PUBLISHED IN THE PARTICULAR JOURNAL, "NATURE
5 JOURNAL."

6 THE COURT: IS THE JOURNAL INCLUDED IN THE
7 CURRICULUM VITAE?

8 MR. METZGER: YES, IT IS. I'LL MOVE ON, YOUR
9 HONOR.

10 THE COURT: THANK YOU.

11 Q BY MR. METZGER: ALL RIGHT. WILL YOU
12 BRIEFLY TELL THE COURT ABOUT YOUR FUNDED RESEARCH:
13 GENERALLY, THE NATURE OF THE RESEARCH, WHAT AGENCIES
14 HAVE FUNDED YOUR RESEARCH.

15 A YES. BRIEFLY, I'VE RECEIVED CONSIDERABLE
16 EXTRAMURAL FUNDING DURING MY TENURE AS A PROFESSOR, BOTH
17 AT BERKELEY AND IN NORTH CAROLINA.

18 THE FUNDED RESEARCH THAT I RECEIVED HAS BEEN
19 IN TWO MAIN AREAS. ONE IS DEVELOPING THE STATISTICAL
20 TOOLS AND MODELS FOR INVESTIGATING EXPOSURE-RESPONSE
21 RELATIONSHIPS. MUCH OF THIS WORK WAS FUNDED BY PRIVATE
22 GROUPS; NIPERA, WHICH IS THE NICKEL PRODUCERS
23 ENVIRONMENTAL RESEARCH ASSOCIATION; AND THE AMERICAN
24 CHEMISTRY COUNCIL.

25 Q IS THAT THE -- IS THE AMERICAN CHEMISTRY
26 COUNCIL THE TRADE ORGANIZATION OF THE CHEMICAL INDUSTRY?

27 A IT IS.

28 I HAVE ALSO RECEIVED CONSIDERABLE FUNDING

1 FROM NATIONAL INSTITUTES OF HEALTH. THESE INCLUDE
2 NIOSH, WHICH IS THE NATIONAL INSTITUTE FOR OCCUPATIONAL
3 SAFETY AND HEALTH; NIHS, WHICH IS THE NATIONAL INSTITUTE
4 FOR ENVIRONMENTAL HEALTH SCIENCES; AND NCI, WHICH IS THE
5 NATIONAL CANCER INSTITUTE.

6 ALL OF THESE WERE RELATED TO DEVELOPMENT AND
7 APPLICATION OF BIOMARKERS.

8 Q ONE MORE QUESTION, AND THEN WE'LL GET ON TO
9 YOUR OPINIONS.

10 IS IT TRUE THAT YOU HAVE PUBLISHED MORE THAN
11 200 PEER-REVIEWED ARTICLES, 15 BOOKS OR BOOK CHAPTERS,
12 AND MORE THAN 200 INVITED PAPERS, LECTURES, AND
13 SEMINARS?

14 A YES.

15 Q ALL RIGHT. NOW LET'S TALK ABOUT YOUR
16 OPINIONS.

17 AND DID I ASK YOU, DR. RAPPAPORT, IF YOU
18 WOULD TESTIFY IN THIS CASE ABOUT THE TOXICOKINETICS OF
19 ACRYLAMIDE?

20 A YES.

21 Q DID YOU AGREE TO DO THAT?

22 A YES.

23 Q ALL RIGHT. FIRST, WILL YOU TELL THE COURT
24 WHAT TOXICOKINETICS IS.

25 A TOXICOKINETICS RELATES TO THE ABSORPTION,
26 DISTRIBUTION, METABOLISM, AND ELIMINATION OF TOXIC
27 SUBSTANCES IN THE BODY.

28 Q AND IS TOXICOKINETICS ONE OF YOUR FIELDS OF

1 EXPERTISE?

2 A YES, IT IS.

3 Q HOW LONG HAS IT BEEN A FIELD OF YOUR
4 EXPERTISE?

5 A I FIRST STARTED INVESTIGATING TOXICOKINETIC
6 PROCESSES IN 1983.

7 Q OKAY. IS TOXICOKINETICS IMPORTANT TO THE
8 STUDY OF HUMAN HEALTH EFFECTS OF CHEMICAL EXPOSURES?

9 A YES, PARTICULARLY WHEN ONE WANTS TO
10 INVESTIGATE THESE EXPOSURE-RESPONSE RELATIONSHIPS.

11 Q AND WHY IS TOXICOKINETICS IMPORTANT TO THE
12 STUDY OF HUMAN CHEMICAL HEALTH EFFECTS?

13 A BECAUSE A NUMBER OF PROCESSES, BIOLOGICAL
14 PROCESSES, ARE SATURABLE; THAT IS, AS THE LEVEL OF THE
15 CHEMICAL IN THE BODY INCREASES TO A CERTAIN POINT, THE
16 CONVERSION OF THAT CHEMICAL TO A METABOLITE CAN CHANGE
17 IN RATE.

18 AND FOR THAT REASON, IT WOULD LEAD TO
19 NONLINEARITIES IN THE EXPOSURE-RESPONSE RELATIONSHIP.

20 Q DR. RAPPAPORT, WHAT'S ACRYLAMIDE?

21 A ACRYLAMIDE IS AN ORGANIC CHEMICAL. IT'S
22 FAIRLY SIMPLE. IT'S PRESENT IN A LOT OF DIETARY
23 PRODUCTS.

24 Q HOW LONG HAVE YOU BEEN STUDYING ACRYLAMIDE
25 OR EXPOSURES TO ACRYLAMIDE?

26 A I'VE BEEN INTERESTED IN ACRYLAMIDE SINCE
27 2002, WHEN IT WAS DETERMINED THAT ACRYLAMIDE WAS A
28 CARCINOGENIC.

1 Q IN FOOD?

2 A IT WAS CARCINOGENIC IN ANIMAL SYSTEMS.

3 Q YEAH. OKAY.

4 ALL RIGHT. AND -- ALL RIGHT. IS THE
5 TOXICOKINETICS OF ACRYLAMIDE IMPORTANT IN ASSESSING THE
6 HUMAN HEALTH EFFECTS OF ACRYLAMIDE?

7 A YES.

8 Q WHY?

9 A IT'S BECAUSE ACRYLAMIDE IS METABOLIZED TO
10 ANOTHER CHEMICAL, CALLED GLYCIDAMIDE. GLYCIDAMIDE IS A
11 MUTAGEN; THAT IS, IT ALTERS DNA IN WAYS THAT ARE
12 DELETERIOUS. IT'S ALSO A CARCINOGEN. AND IT IS WIDELY
13 RECOGNIZED AS BEING A VERY HAZARDOUS CHEMICAL.

14 Q ALL RIGHT. LET'S START AT THE BEGINNING, IF
15 WE COULD. WOULD YOU TELL THE COURT BRIEFLY HOW
16 ACRYLAMIDE IS FORMED IN FOODS.

17 A THERE'S A CHEMICAL REACTION THAT'S REFERRED
18 TO AS THE MAILLARD REACTION. AND IT'S A REACTION OF TWO
19 CHEMICALS. ONE IS ASPARAGINE, WHICH IS --

20 Q ASPARAGINE?

21 A ASPARAGINE, WHICH IS AN AMINO ACID. AND IT
22 REACTS WITH A SUGAR, USUALLY GLUCOSE OR FRUCTOSE. AND
23 THE PRODUCT OF THIS REACTION IS ACRYLAMIDE.

24 Q OKAY. IN WHAT TYPES OF FOODS IS ACRYLAMIDE
25 FOUND?

26 A IT'S FOUND IN A VARIETY OF FOODS; NOTABLY,
27 IN -- WELL, I SHOULD MENTION THAT THE MAILLARD REACTION
28 REQUIRES HEAT.

1 Q AH.

2 A SO IT'S ONLY IN FOODS THAT HAVE BEEN HEATED
3 TO A CERTAIN TEMPERATURE THAT YOU'LL FIND ACRYLAMIDE.
4 SO YOU FIND IT IN THINGS LIKE POTATO CHIPS AND FRENCH
5 FRIES. IT'S ALSO PRESENT IN COFFEE. IT'S PRESENT IN
6 CIGARETTE SMOKE, AS WELL.

7 Q HOW IS IT PRESENT IN COFFEE?

8 A IT'S PRODUCED DURING THE ROASTING OF THE
9 BEANS.

10 Q ALL RIGHT. YOU'VE TOLD US THAT ACRYLAMIDE
11 IS A CARCINOGEN. HOW IS IT KNOWN -- HOW DO YOU KNOW
12 THAT ACRYLAMIDE -- WELL, FIRST OF ALL, LET ME BACK UP.

13 IS A CARCINOGEN A CHEMICAL OR SUBSTANCE THAT
14 CAN CAUSE CANCER?

15 A YES, IT IS.

16 Q ALL RIGHT. HOW IS IT THAT YOU KNOW THAT
17 ACRYLAMIDE IS A CARCINOGEN?

18 A BECAUSE I'VE REVIEWED THE SEVERAL PAPERS
19 THAT DESCRIBE TESTS IN ANIMALS WHERE ACRYLAMIDE WAS
20 ADMINISTERED, AND THE ANIMALS HAD SIGNIFICANT EXCESS OF
21 TUMORS AT DIFFERENT SITES.

22 Q DO YOU KNOW A GENTLEMAN BY THE NAME OF JAMES
23 HUFF?

24 A I HAVE MET HIM, YES.

25 Q OKAY. AND ARE YOU AWARE THAT HE WILL BE
26 TESTIFYING ABOUT THE ANIMAL CARCINOGENICITY OF
27 ACRYLAMIDE IN THIS CASE?

28 A YES.

1 Q WE'LL DEFER THAT FOR HIM, THEN.

2 NOW, YOU MENTIONED METABOLISM. WOULD YOU
3 EXPLAIN WHAT METABOLISM IS IN THIS CONTEXT.

4 A YES. WHEN WE INGEST FOOD, THE FOOD IS
5 METABOLIZED. WE HAVE ENZYMES IN OUR BODY THAT ARE
6 DESIGNED TO CONVERT THE CHEMICALS FROM FOODS FROM ONE
7 FORM TO ANOTHER -- TO PROVIDE ENERGY, TO PROVIDE THE
8 OTHER ESSENTIAL MOLECULES WE NEED FOR LIFE.

9 AND AS PART OF THIS METABOLISM PROCESS,
10 SOMETIMES TOXIC CHEMICALS CAN BE FORMED.

11 Q SO ENZYMES IN THE BODY METABOLIZE CERTAIN
12 CHEMICALS TO BECOME MORE TOXIC CHEMICALS?

13 A THEY DO. I DON'T THINK THEY DO IT ON
14 PURPOSE.

15 Q BUT THAT'S WHAT THEY DO?

16 A BUT THAT'S ESSENTIALLY WHAT HAPPENS IN SOME
17 CASES.

18 Q OKAY. AND I THINK YOU MENTIONED THAT
19 ACRYLAMIDE IS METABOLIZED TO GLYCIDAMIDE?

20 A YES.

21 Q WOULD YOU TELL US ABOUT THAT, WHAT GOES ON.

22 A YES. WELL, THERE'S A PARTICULAR ENZYME
23 CALLED CYTOCHROME P450 2E1. IT'S A HUGE NAME FOR THIS
24 ENZYME. AND IT SPECIFICALLY TAKES SMALL MOLECULES, LIKE
25 ACRYLAMIDE, AND CONVERTS THEM INTO FORMS THAT ARE CALLED
26 EPOXIDES. AND GLYCIDAMIDE IS AN EPOXIDE.

27 Q WHAT IS AN EPOXIDE?

28 A AN EPOXIDE HAS AN UNSTABLE THREE-ELEMENT

1 RING. IT'S GOT TWO CARBONS AND AN OXYGEN, IN FORM. AND
2 BECAUSE IT'S UNSTABLE, THIS MOLECULE WANTS TO REACT WITH
3 OTHER MOLECULES. AND IN SO DOING, IT CAN REACT WITH DNA
4 OR PROTEINS AND OTHER MOLECULES IN THE BODY.

5 Q ALL RIGHT. SO FROM THIS ENZYME WITH THE
6 COMPLICATED NAME OR NUMBERS, ACRYLAMIDE IS METABOLIZED
7 TO GLYCIDAMIDE. WHERE DOES THAT HAPPEN?

8 A IT HAPPENS MOSTLY IN THE LIVER. THE LIVER
9 IS THE CHEMICAL FACTORY FOR THE BODY.

10 Q AND ONCE THAT METABOLISM OCCURS AND
11 GLYCIDAMIDE IS PRODUCED, MOSTLY IN THE LIVER, WHAT
12 HAPPENS NEXT?

13 A WELL, THE GLYCIDAMIDE IS DISTRIBUTED
14 THROUGHOUT THE BODY. IT ENTERS THE BLOOD AFTER IT
15 LEAVES THE LIVER. IT CAN BE DISTRIBUTED TO ALL THE
16 TISSUES, AND IT'S CAPABLE OF REACTING IN ALL THESE
17 TISSUES TO PRODUCE DAMAGE.

18 Q NOW, YOU MENTIONED, I THINK -- I THINK YOU
19 SAID -- IS GLYCIDAMIDE CARCINOGENIC?

20 A YES, IT IS.

21 Q HOW DO YOU KNOW THAT GLYCIDAMIDE IS
22 CARCINOGENIC?

23 A IT'S BEEN TESTED. I THINK THE NATIONAL
24 TOXICOLOGY PROGRAM TESTED GLYCIDAMIDE IN MICE AND RATS
25 AND FOUND THAT IT WAS QUITE CARCINOGENIC.

26 Q OKAY. WHAT IS GENOTOXICITY?

27 A GENOTOXICITY REFERS TO THE ABILITY OF
28 CERTAIN CHEMICALS TO ALTER DNA AND, IN SO DOING, PRODUCE

1 MUTATIONS WHICH CAN GO ON TO BECOME CANCER OR OTHER
2 DELETERIOUS EFFECTS.

3 Q OKAY. IS GLYCIDAMIDE A GENOTOXIC CHEMICAL?

4 A YES.

5 Q HOW DO YOU KNOW THAT?

6 A BECAUSE GLYCIDAMIDE REACTS WITH DNA TO
7 PRODUCE THESE THINGS CALLED ADDUCTS. AND THESE DNA
8 ADDUCTS HAVE BEEN MEASURED IN MANY TISSUES FROM ANIMALS
9 THAT HAVE BEEN ADMINISTERED GLYCIDAMIDE OR ACRYLAMIDE.

10 Q ALL RIGHT. IS THE GENOTOXICITY OF
11 GLYCIDAMIDE IMPORTANT TO THE CARCINOGENICITY OF
12 ACRYLAMIDE?

13 A YES.

14 Q WHY?

15 A BECAUSE ACRYLAMIDE IS CONVERTED TO
16 GLYCIDAMIDE IN THE BODY. GLYCIDAMIDE IS A GENOTOXIC
17 CARCINOGEN. THEREFORE ACRYLAMIDE CAN EXERT ITS
18 CARCINOGENICITY THROUGH THIS MECHANISM, THE PRODUCTION
19 OF GLYCIDAMIDE.

20 Q ALL RIGHT. NOW, YOU MENTIONED THAT
21 GLYCIDAMIDE IS DISTRIBUTED TO DIFFERENT TISSUES IN THE
22 BODY. WHAT DO YOU MEAN BY "TISSUES IN THE BODY"?

23 A WELL, THE BLOOD IS A TISSUE. THE BRAIN,
24 MUSCLES, LUNGS, HEART, VISCERAL ORGANS -- THESE ARE ALL
25 TISSUES. AND GLYCIDAMIDE IS VERY EFFICIENTLY
26 TRANSPORTED BY THE BLOOD TO ALL OF THESE SITES, THESE
27 OTHER TISSUES.

28 Q HOW DO YOU KNOW THAT?

1 A BECAUSE IT'S BEEN MEASURED IN ANIMALS IN
2 THESE DIFFERENT TISSUES.

3 Q AND HOW EFFICIENTLY IS GLYCIDAMIDE
4 DISTRIBUTED IN THE BODY?

5 A VERY EFFICIENTLY. IT'S EXTREMELY WATER
6 SOLUBLE. IT'S TRANSPORTED WITH THE BODY WATER, AND IT
7 PENETRATES TISSUES QUITE READILY.

8 Q AND OF WHAT SIGNIFICANCE IS IT TO HUMAN
9 HEALTH THAT GLYCIDAMIDE IS SO EFFICIENTLY DISTRIBUTED TO
10 THESE DIFFERENT TISSUES OR ORGANS IN THE BODY?

11 A WELL, THE POTENTIAL IS THAT GLYCIDAMIDE CAN
12 CAUSE GENOTOXIC EFFECTS, INCLUDING CANCER, IN ANY TISSUE
13 IN THE BODY.

14 Q ALL RIGHT. NOW, DR. RAPPAPORT, I WANT TO
15 ASK YOU -- WE'RE GOING TO START TALKING ABOUT ADDUCTS.
16 LET ME PREFACE THIS: DOES GLYCIDAMIDE FORM ADDUCTS?

17 A YES, IT DOES.

18 Q ALL RIGHT. AND HAVE YOU PUBLISHED
19 PEER-REVIEWED ARTICLES REGARDING THE FORMATION OF
20 ADDUCTS?

21 A YES.

22 Q ABOUT HOW MANY?

23 A 40 OR 50.

24 Q THIS HAS BEEN A MAJOR AREA OF YOUR RESEARCH?

25 A YES.

26 Q OKAY. AND ARE THOSE ARTICLES LISTED IN YOUR
27 CURRICULUM VITAE?

28 A THEY ARE.

1 Q ALL RIGHT. WHY HAVE YOU FOCUSED SO MUCH OF
2 YOUR RESEARCH AND PUBLICATION ON ADDUCTS?

3 A AGAIN, THESE ADDUCTS REPRESENT THE
4 FINGERPRINTS FROM EXPOSURE TO THESE TOXIC SUBSTANCES,
5 LIKE GLYCIDAMIDE, THAT ARE DIFFICULT TO MEASURE
6 DIRECTLY.

7 Q OKAY. IS YOUR LABORATORY ONE THAT HAS
8 IDENTIFIED AND QUANTIFIED DIFFERENT TYPES OF ADDUCTS?

9 A YES.

10 Q CAN YOU TELL THE COURT ABOUT SOME OF THE
11 MAJOR LABORATORIES THAT DO THIS ADDUCT RESEARCH.

12 A YES. THERE ARE RELATIVELY FEW. I WOULD SAY
13 THE MAJOR LABORATORY IN EUROPE IS ONE OF MARGARETA
14 TORNQVIST, AT STOCKHOLM UNIVERSITY. THEY WERE THE ONES
15 THAT GOT ME INTERESTED IN ADDUCTS IN THE 1980S. I KNEW
16 DR. TORNQVIST WHEN SHE WAS A PH.D. STUDENT THERE.

17 Q OKAY. THAT'S T-O-R-N-Q-V-I-S-T; IS THAT
18 CORRECT?

19 A YES.

20 Q ALL RIGHT. AND HAS DR. TORNQVIST'S
21 LABORATORY BEEN AT THE FOREFRONT OF THE RESEARCH OF
22 ACRYLAMIDE AND GLYCIDAMIDE ADDUCTS?

23 A YES, VERY MUCH SO.

24 Q HAVE YOU VISITED THAT LABORATORY AND
25 DISCUSSED THAT RESEARCH WITH DR. TORNQVIST?

26 A I HAVE.

27 Q SO WHAT ARE THE DIFFERENT TYPES OF
28 SUBSTANCES TO WHICH ADDUCTS BIND?

1 A WELL, THEY BIND TO ANY MOLECULE IN THE BODY
2 THAT HAS THE PROPER CHEMISTRY. IN CHEMICAL TERMS, THE
3 MOLECULES ARE CALLED NUCLEOPHILES. THEY REACT WITH
4 THESE REACTIVE CHEMICALS THAT ARE CALLED ELECTROPHILES.
5 AND CHEMISTS ALWAYS HAVE NAMES FOR EVERYTHING.

6 BUT THE POINT IS THAT THE BODY IS FULL OF
7 NUCLEOPHILES, MOSTLY IN THE FORM OF DNA AND PROTEINS.

8 Q OKAY. DID YOU SELECT A GRAPHIC TO SHOW
9 ADDUCTS?

10 A I DID. I THOUGHT IT WOULD BE HELPFUL JUST
11 TO SEE, ON THE ONE HAND, THE REACTION OF GLYCIDAMIDE --
12 I MEAN, OF ACRYLAMIDE TO GLYCIDAMIDE, WHICH IS SHOWN AT
13 THE UPPER LEFT CORNER. THEY'RE BOTH VERY SIMPLE
14 MOLECULES. AND IT'S THIS CYTOCHROME P450 2E1 THAT
15 CATALYZES THE REACTION BETWEEN -- OR REACTION OF
16 ACRYLAMIDE TO GET GLYCIDAMIDE.

17 THEN THE GLYCIDAMIDE, WHICH IS THE EPOXIDE
18 ON THE RIGHT -- YOU SEE THAT CHARACTERISTIC THREE-ATOM
19 RING; IT HAS AN OXYGEN AND THEN TWO CARBONS. THAT'S
20 UNSTABLE. AND WHEN IT COMES IN CONTACT WITH A
21 NUCLEOPHILE, LIKE A DNA BASE --

22 AND AT THE BOTTOM ARE THREE DIFFERENT BASES
23 OF DNA. AND THEY SHOW THIS REACTION PRODUCT OF THE DNA
24 BASE -- FIRST, 1, BEING GUANINE; AND THE SECOND, 2,
25 BEING ADENINE -- TO PRODUCE THESE ADDUCTS.

26 Q IF YOU SAY SO.

27 HAS THE ABILITY OF ACRYLAMIDE TO INDUCE
28 HEMOGLOBIN ADDUCTS -- LET ME BACK UP.

1 IS ONE OF THE TYPES OF ADDUCTS THAT
2 ACRYLAMIDE CAN FORM, OR GLYCIDAMIDE, A HEMOGLOBIN
3 ADDUCT?

4 A YES.

5 Q AND THAT'S AN ADDUCT THAT FORMS ON
6 HEMOGLOBIN WITHIN -- IS THAT RED BLOOD CELLS?

7 A YES, INSIDE THE BLOOD CELLS.

8 Q OKAY. HAS THE ABILITY OF ACRYLAMIDE TO
9 INDUCE HEMOGLOBIN ADDUCTS BEEN STUDIED IN HUMANS?

10 A YES, IT HAS. AND AGAIN, DR. TORNQVIST'S
11 LABORATORY WAS THE FIRST TO DO THIS.

12 AND I SHOULD MENTION THAT ACRYLAMIDE IS ALSO
13 CAPABLE OF FORMING ADDUCTS WITH HEMOGLOBIN. IT IS ALSO
14 A WEAK ELECTROPHILE, AND IT DOES BIND TO HEMOGLOBIN. IT
15 DOES NOT BIND TO DNA, HOWEVER, SO IT IS NOT INHERENTLY
16 GENOTOXIC. GLYCIDAMIDE BINDS TO BOTH HEMOGLOBIN AND TO
17 DNA.

18 Q SO IF I UNDERSTAND, IN ORDER TO BIND TO DNA
19 AND CAUSE POTENTIAL -- THE POTENTIAL FOR CANCER, THE
20 ACRYLAMIDE HAS TO BE METABOLIZED TO GLYCIDAMIDE; IS THAT
21 CORRECT?

22 A YES, THAT'S CORRECT.

23 Q ALL RIGHT. NOW, CAN YOU TELL US WHAT THE
24 SIGNIFICANCE IS OF THE STUDIES THAT HAVE BEEN DONE
25 REGARDING THE INDUCTION OF HEMOGLOBIN ADDUCTS IN HUMANS.

26 A THE SIGNIFICANCE, IN MY OPINION, IS THAT THE
27 STUDIES HAVE SHOWN THAT THERE IS A VERY CONSISTENT
28 INCREASE IN THE PRODUCTION OF THESE ADDUCTS WITH DIETARY

1 EXPOSURE TO ACRYLAMIDE.

2 Q TELL US A LITTLE ABOUT THOSE STUDIES. HOW
3 IS THIS DONE, THAT THAT WAS ASCERTAINED?

4 A THERE WERE -- THERE ARE SEVERAL STUDIES.
5 THE MAJOR ONES ARE THE ONES THAT I CITED HERE, WHICH
6 WERE TIMOTHY FENNELL, WHO DID A CLINICAL TRIAL WHERE
7 THEY ADMINISTERED ACRYLAMIDE TO HUMAN SUBJECTS,
8 VOLUNTEER SUBJECTS. AND THEN THEY MEASURED THE ADDUCTS
9 THAT HAD BEEN PRODUCED FROM THIS EXPERIMENT IN THE
10 SUBJECTS.

11 AND THEY SHOWED, OVER THE WHOLE DOSE
12 RANGE -- WHICH WAS UP TO 3 MILLIGRAMS PER KILOGRAM OF
13 BODY WEIGHT -- THAT THERE WAS A CONSISTENT LINEAR
14 INCREASE IN THE PRODUCTION OF ADDUCTS.

15 Q LET ME JUST INTERRUPT YOU. WHEN YOU SAY A
16 "CONSISTENT LINEAR INCREASE," WHAT DOES THAT MEAN? AND
17 IF IT WOULD HELP TO ILLUSTRATE THAT, FEEL FREE TO USE
18 THE BOARD. YOU ARE A PROFESSOR.

19 A OKAY. I'D BE HAPPY TO.

20 SO WE'LL CALL THIS THE ADMINISTERED DOSE OF
21 ACRYLAMIDE. AND HERE WE'LL LOOK AT THE ADDUCTS
22 PRODUCTION.

23 AND WHAT YOU SEE WITH THE WORK THAT WAS DONE
24 IN ALL OF THE STUDIES, THAT AS THE ADMINISTERED DOSE OF
25 ACRYLAMIDE INCREASES, THE LEVEL OF ADDUCTS WOULD
26 INCREASE, AS WELL, IN A LINEAR FASHION. SO THAT IF YOU
27 HAD TWICE AS MUCH ADMINISTERED DOSE, YOU'D HAVE TWICE AS
28 MUCH OF THE ADDUCTS THAT WOULD BE PRODUCED.

1 SO IT'S A SIMPLE STRAIGHT-LINE RELATIONSHIP.
2 THAT'S WHAT WE MEAN BY "LINEAR."

3 Q OKAY. AND I THINK I INTERRUPTED YOU. YOU
4 WERE GOING TO TELL US ABOUT THE VIKSTROM STUDY.

5 A YES. THE VIKSTROM STUDY WAS THE OTHER MAJOR
6 STUDY THAT WAS DONE. IN THIS CASE, HUMANS WERE FED A
7 DIET OF DIFFERENT FOODS THAT HAD BEEN HEATED AND HAD
8 KNOWN AMOUNTS OF ACRYLAMIDE IN THEM.

9 THE LEVELS OF DOSING IN THIS CASE WERE LOWER
10 THAN THOSE THAT FENNELL HAD USED, AND THEY SHOWED THE
11 SAME RESPONSE: THAT AS YOU INCREASE THE AMOUNT OF
12 DIETARY CONSUMPTION, THEY MEASURED AN INCREASE IN THE
13 ADDUCT LEVELS.

14 Q AND AT WHAT DOSE LEVELS WERE THESE?

15 A IN THE LOWEST LEVEL -- THE LOWEST DOSE GROUP
16 OF VIKSTROM, I THINK IT WAS .0 -- .011 MILLIGRAMS PER
17 KILOGRAM.

18 Q AND IS THAT A DOSE THAT PEOPLE HAVE IN A
19 DIET?

20 A IT'S VERY CLOSE TO WHAT PEOPLE WOULD HAVE IN
21 A DIET IF THEY WERE EATING FOODS THAT CONTAINED
22 ACRYLAMIDE, SUCH AS FRENCH FRIES OR DIFFERENT FOODS.

23 Q OKAY. IS THE METABOLISM OF ACRYLAMIDE
24 AFFECTED BY THE DOSE IN HUMANS?

25 A THE RATE OF METABOLISM IS NOT AFFECTED BY
26 THE DOSE. AND THAT, AGAIN -- IT GOES BACK TO THIS
27 LINEAR RELATIONSHIP. WE SEE THAT OVER THE DOSE RANGE
28 THAT HUMANS CAN RECEIVE, WHICH IS LESS THAN 3 MILLIGRAMS

1 PER KILOGRAM OF BODY WEIGHT, THE PRODUCTION OF
2 GLYCIDAMIDE IS -- IT OCCURS AT THE SAME RATE.

3 Q OKAY. HOW DOES THE METABOLISM OF ACRYLAMIDE
4 AND GLYCIDAMIDE IN HUMANS COMPARE TO THAT OF RODENTS?

5 A IT'S COMPARABLE. I'D SAY THE BEST EVIDENCE
6 THAT WE HAVE OF THE SYSTEMATIC DOSES GIVEN, FROM
7 MEASUREMENTS OF THESE HEMOGLOBIN ADDUCTS -- AND
8 TORNQVIST'S LABORATORY HAS USED ALL THE DATA FROM THEIR
9 LABORATORY, AND ALSO FROM FENNELLS STUDIES, TO INDICATE
10 THAT HUMANS ACTUALLY HAVE HIGHER DOSES OF ACRYLAMIDE AND
11 GLYCIDAMIDE THAN ANIMALS, BETWEEN TWO AND FIVE TIMES
12 GREATER, BASED UPON THE PRODUCTION OF THESE ADDUCTS.

13 MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT AND MOVE
14 TO STRIKE THE DISCUSSION OF THE TORNQVIST LABORATORY.
15 NONE OF THOSE MATERIALS WERE PRODUCED AS PART OF DR.
16 RAPPAPORT'S RELIANCE MATERIALS, AND NONE OF THEM ARE
17 CITED IN THE SUMMARY OF OPINIONS THAT HE'S PROVIDED.

18 THE COURT: OBJECTION OVERRULED.

19 Q BY MR. METZGER: YOU MENTIONED THE TERM
20 "SYSTEMATIC DOSE." WHAT IS THAT?

21 A IT'S THE DOSE OF ACRYLAMIDE OR GLYCIDAMIDE
22 THAT'S PRESENT IN THE SYSTEMATIC CIRCULATION WITHIN THE
23 BLOOD.

24 Q OKAY. I THINK YOU REFERRED TO "DOSIMETRY"
25 OR "DOSIMETER." WHAT IS THAT, IN THIS CONTEXT?

26 A WELL, YOU COULD THINK OF THESE HEMOGLOBIN
27 ADDUCTS OF ACRYLAMIDE AND GLYCIDAMIDE AS DOSIMETERS. AS
28 THE DOSE INCREASES, THE CONCENTRATIONS OF THESE ADDUCTS

1 ALSO INCREASES. SO THEY'RE GIVING YOU INFORMATION ABOUT
2 THE SYSTEMATIC DOSE BECAUSE THEY'RE MEASURED IN THE
3 BLOOD.

4 Q IS MEASURING THESE ADDUCTS OF ACRYLAMIDE AND
5 GLYCIDAMIDE A MEANS OF ACCURATELY ASSESSING HUMAN
6 EXPOSURE TO ACRYLAMIDE AND GLYCIDAMIDE?

7 A IT IS A MEASURE OF THE SYSTEMATIC EXPOSURE.
8 THAT'S THE EXPOSURE THAT REACHES THE BLOOD, YES.

9 Q OKAY. AND IS PART OF THE RESEARCH IN
10 ADDUCTS USING ADDUCTS AS DOSIMETERS?

11 A YES.

12 Q WHY IS THAT DONE? WHAT'S THE UTILITY OF
13 THAT?

14 A AGAIN, IT GOES BACK TO THE FACT THAT WE
15 CAN'T MEASURE GLYCIDAMIDE EASILY IN THE BLOOD, BUT WE
16 CAN MEASURE THESE ADDUCTS. AND THEY TELL US HOW MUCH
17 GLYCIDAMIDE WAS THERE OVER A CERTAIN PERIOD OF TIME.

18 THE COURT: PROFESSOR, LET ME ASK YOU THIS. DOES
19 GLYCIDAMIDE NATURALLY OCCUR IN HUMAN METABOLISM,
20 IRRESPECTIVE OF DIET?

21 THE WITNESS: IT REQUIRES ACRYLAMIDE IN ORDER TO
22 BE FORMED. SO IF THE HUMAN BEING RECEIVES ACRYLAMIDE
23 FROM ANY SOURCE -- IT COULD BE, FOR EXAMPLE, CIGARETTE
24 SMOKE -- THEN GLYCIDAMIDE WOULD BE PRODUCED, AS WELL.

25 I THINK MOST OF THE SOURCES OF ACRYLAMIDE
26 EXPOSURE TO HUMANS ARE FROM DIET. THERE ARE SOME
27 OCCUPATIONAL SETTINGS WHERE PEOPLE HAVE INHALED
28 ACRYLAMIDE, AS WELL, AND THEN PRODUCED GLYCIDAMIDE.

1 THE COURT: AND GLYCIDAMIDE NEEDS ACRYLAMIDE TO BE
2 PRODUCED?

3 THE WITNESS: YES, I THINK THAT'S CORRECT. I'M
4 NOT SURE THAT GLYCIDAMIDE IS PRODUCED FROM ANY OTHER
5 PRECURSOR MOLECULE.

6 THE COURT: ALL RIGHT. THANK YOU.

7 WHAT KIND OF OCCUPATION HAS A -- COULD
8 CREATE ACRYLAMIDE? COULD THAT BE --

9 THE WITNESS: THERE ARE CERTAIN ACRYLAMIDE-
10 CONTAINING PRODUCTS THAT ARE USED, FOR EXAMPLE, TO
11 SOLIDIFY STRUCTURES.

12 THE INITIAL MEASUREMENT OF ADDUCTS IN HUMAN
13 BEINGS WAS FROM A TUNNEL THAT WAS BEING PRODUCED IN THE
14 NORTH SEA. AND THE WORKERS FROM THAT TUNNEL WERE HAVING
15 SOME PROBLEMS.

16 AND MARGARETA TORNQVIST'S LABORATORY
17 RECEIVED BLOOD FROM THOSE PERSONS AND FOUND OUT THAT
18 THEY ACTUALLY HAD QUITE HIGH LEVELS OF ADDUCTS.

19 THE COURT: SO IT WAS SOME MATERIAL THAT WAS USED
20 DURING CONSTRUCTION?

21 THE WITNESS: YES. IT WAS USED IN THE PRODUCTION
22 OF A POLYMER THAT WAS USED TO REINFORCE THE WALLS OF
23 THIS TUNNEL THAT WAS BEING PRODUCED.

24 THE COURT: ALL RIGHT. THANK YOU.

25 Q BY MR. METZGER: DR. RAPPAPORT, WHAT IS THE
26 SIGNIFICANCE OF SYSTEMATIC DOSES OF ACRYLAMIDE AND
27 GLYCIDAMIDE BEING GREATER IN HUMANS THAN IN RATS?

28 A WELL, IT WOULD JUST INDICATE TO ME THAT

1 GLYCIDAMIDE IS PRODUCED IN HUMANS. AND BECAUSE IT IS
2 CARCINOGENIC IN RODENTS, AND THE SYSTEMATIC DOSE IS AT
3 OR GREATER THAN WHAT THE RODENTS RECEIVED THAN IN
4 COMPARABLE DOSES IN HUMANS, ONE WOULD SUSPECT THAT THERE
5 IS A RISK OF CANCER.

6 THE COURT: LET ME ASK, TO FOLLOW UP ON MY
7 PREVIOUS QUESTION: ASIDE FROM ACRYLAMIDE, IS THERE ANY
8 OTHER SUBSTANCE OR CHEMICAL THAT PRODUCES GLYCIDAMIDE?

9 THE WITNESS: I'M NOT AWARE OF IT, YOUR HONOR.

10 THE COURT: THANK YOU.

11 Q BY MR. METZGER: ALL RIGHT. DR. RAPPAPORT,
12 GIVEN WHAT YOU'VE TOLD US SO FAR ABOUT THE METABOLISM OF
13 ACRYLAMIDE TO GLYCIDAMIDE, THE DISTRIBUTION, AND ITS
14 ABILITY TO FORM ADDUCTS, WHAT IS THE SIGNIFICANCE OF
15 THOSE TOXICOKINETIC PROPERTIES TO HUMAN HEALTH?

16 A WELL, IN RISK ASSESSMENT, THE DEFAULT
17 ASSUMPTION IS OFTEN THAT YOU HAVE A LOW-DOSE LINEAR
18 MODEL OF CARCINOGENICITY THAT IS CANCER INDUCTION.

19 AND ALL OF THE EVIDENCE SUGGESTS THAT IN
20 HUMANS, AT DOSES BELOW 3 MILLIGRAMS PER KILOGRAM --
21 WHICH IS THE VAST MAJORITY OF ALL DOSES IN HUMANS --
22 THERE IS NO NONLINEARITY INVOLVED IN THE TOXICOKINETICS.

23 AND IT'S ENTIRELY CONSISTENT WITH THIS
24 ACCEPTED MODEL OF -- LOW-DOSE LINEAR MODEL OF CANCER
25 INDUCTION IN HUMANS.

26 Q OKAY. NOW, IS ONE OF THE THINGS THAT YOU
27 DID FOR THIS CASE WAS TO DO SOME STATISTICAL ANALYSES OF
28 THE DATA TO ASSESS WHETHER, IN FACT, THE RELATIONSHIPS

1 THAT YOU DESCRIBED ARE TRULY LINEAR?

2 A NOT IN HUMANS, BUT IN ANIMAL STUDIES, YES.

3 Q OKAY. WHY DON'T WE GO TO A TABLE THAT'S IN
4 YOUR REPORT.

5 AND IF WE COULD DISPLAY THAT. PERHAPS YOU
6 COULD IDENTIFY WHICH REPORT IT IS, BY EXHIBIT NUMBER.

7 IS WHAT'S NOW DISPLAYED AS TABLE 1 -- DATA
8 FROM ABRAMSSON-ZETTERBERG, ET AL., SHOWING NUMBERS OF
9 MICRONUCLEATED ERYTHROCYTES OF MICE -- IS THIS A TABLE
10 THAT YOU PREPARED?

11 A YES, I THINK THIS IS. YES, IT'S FROM THE
12 FIRST REPORT THAT I SUBMITTED TO YOU. I CAN'T -- LET ME
13 FIND IT HERE.

14 Q IS IT EXHIBIT 316?

15 A YES, 316.

16 MR. METZGER: OKAY. YOUR HONOR, IN SOME CASES,
17 COURTS HAVE ADMITTED IN EVIDENCE JUST DATA, NOT -- CAN
18 I -- I'LL MAKE AN -- MAY I OFFER THE DATA TABLE IN
19 EVIDENCE, SO THE RECORD IS CLEAR?

20 THE COURT: ARE YOU OFFERING THE DATA TABLE 1 TO
21 BE MARKED AS AN EXHIBIT?

22 MR. METZGER: IT IS WITHIN EXHIBIT 316, BUT NOT
23 SEPARATELY. SO WE CAN MAKE IT A SEPARATE EXHIBIT, JUST
24 FOR THE DATA.

25 THE COURT: IS IT PART OF 316?

26 MR. METZGER: YES.

27 THE COURT: THEN 316A?

28 MR. METZGER: YES, WE'LL MAKE IT 316A. I THINK IT

1 WILL HELP.

2 (EXHIBIT 316A MARKED FOR
3 IDENTIFICATION.)

4 MR. SCHURZ: YOUR HONOR, WE OBJECT ON HEARSAY
5 GROUNDS. THIS IS A TABLE THAT DR. RAPPAPORT HAS
6 PURPORTED TO REFLECT FROM THE ABRAMSSON-ZETTERBERG
7 ARTICLE, AND WE WILL BE TALKING ABOUT IT LATER.

8 IT'S HEARSAY. THERE IS NO BASIS FOR
9 ACCEPTING IT INTO EVIDENCE. AND WE HAVE QUESTIONS WITH
10 RESPECT TO HOW THIS TABLE IS SET FORTH IN DR.
11 RAPPAPORT'S MATERIALS.

12 THE COURT: OBJECTION IS SUSTAINED.

13 Q BY MR. METZGER: ALL RIGHT. WELL, LET'S
14 JUST TALK ABOUT IT, THEN, DR. RAPPAPORT. I MAY ASK YOU
15 TO READ ALL THE NUMBERS INTO THE RECORD BECAUSE THE DATA
16 TABLE APPARENTLY WILL NOT BE AN EXHIBIT. SO IT MAY TAKE
17 A WHILE.

18 WELL, WOULD YOU TELL US WHAT -- START OUT:
19 WHAT IS IT THAT YOU DID IN GENERATING THIS TABLE?

20 A THERE WERE TWO STUDIES THAT I INVESTIGATED
21 IN WHICH ACRYLAMIDE WAS ADMINISTERED TO MICE. AND THE
22 MICE PRODUCED MICRONUCLEATED RED BLOOD CELLS.

23 Q WHAT IS THAT?

24 A THE MICRONUCLEI ARE PIECES -- WELL, IT'S
25 EITHER A CHROMOSOME OR A PIECE OF CHROMOSOME THAT'S
26 RETAINED IN THE RED BLOOD CELL. AND IT'S WIDELY
27 REGARDED AS A -- IT'S A GOOD MEASURE OF GENOTOXIC
28 EFFECT.

1 SO THERE IS A SPECIFIC ASSAY CALLED A MOUSE
2 MICRONUCLEUS ASSAY, IN WHICH THEY COUNT THE NUMBERS OF
3 MICRONUCLEATED RED BLOOD CELLS. THAT'S A MEASURE OF THE
4 ABILITY OF A PARTICULAR DOSE OF A SUBSTANCE TO PRODUCE
5 THIS GENOTOXIC EFFECT.

6 AND IN THIS PARTICULAR STUDY, WHICH WAS
7 CONDUCTED IN SWEDEN, THEY INJECTED DIFFERENT AMOUNTS OF
8 ACRYLAMIDE A SINGLE TIME INTO MICE. THERE WERE FIVE
9 MICE PER GROUP.

10 AND AS YOU CAN SEE, THERE WERE SEVEN
11 DIFFERENT GROUPS: A CONTROL GROUP, THAT HAD NO
12 ADMINISTRATION OF ACRYLAMIDE; AND THEN DOSES
13 REPRESENTING 1, 3, 6, 12, 24, AND 30 MILLIGRAMS OF
14 ACRYLAMIDE PER KILOGRAM OF BODY WEIGHT.

15 Q OKAY. SO THE MICE ARE GIVEN ACRYLAMIDE BY
16 AN INJECTION?

17 A YES. IT'S CALLED IP, INTRAPERITONEAL,
18 INJECTION.

19 Q THEN THE MICE GET THESE MICRONUCLEI IN THE
20 BLOOD CELLS, AND THEY'RE COUNTED BY MEANS OF THIS ASSAY?

21 A YES. THEY'RE COUNTED VERY EFFICIENTLY.

22 Q OKAY. SO IN THE FIRST COLUMN YOU HAVE THE
23 ADMINISTERED DOSE, WHICH YOU JUST EXPLAINED TO US.

24 AND THE NEXT COLUMN, IT SAYS "NUMBER OF
25 CELLS ANALYZED." WHAT IS THAT?

26 A SO THESE ARE THE NUMBER OF RED BLOOD CELLS
27 THAT WERE COUNTED TO DETERMINE WHETHER THEY HAD
28 MICRONUCLEI PRESENT.

1 Q OKAY.

2 A AND YOU CAN SEE THERE'S ROUGHLY 1 TO
3 2 MILLION CELLS THAT WERE COUNTED.

4 Q OKAY. AT EACH DOSE LEVEL?

5 A YES, FOR THE FIVE ANIMALS IN EACH GROUP.

6 Q OKAY. AND THEN THE THIRD COLUMN IS THE
7 NUMBER OF MICRONUCLEI THAT WERE COUNTED; IS THAT
8 CORRECT?

9 A THE NUMBER OF THESE RED BLOOD CELLS THAT
10 CONTAINED DETECTABLE MICRONUCLEI.

11 Q OKAY. AND THEN THE LAST COLUMN IS THE
12 NUMBER OF MICRONUCLEI PER 1,000 CELLS?

13 A YES. AND THAT'S SIMPLY THE THIRD COLUMN,
14 THE NUMBER OF MICRONUCLEI, DIVIDED BY THE SECOND COLUMN,
15 WHICH IS THE NUMBER OF CELLS, AND THEN TIMES 1,000.

16 Q OKAY. SO IF WE LOOK AT THE FIRST COLUMN AND
17 THE LAST COLUMN, THE FIRST ROW IS THE CONTROL; CORRECT?

18 A YES. ZERO DOSE; CORRECT.

19 Q OKAY. AND FOR THE ZERO DOSE, THERE WERE
20 1.1871 MICRONUCLEI PER 1,000 CELLS; IS THAT RIGHT?

21 A THAT'S CORRECT.

22 Q COULD YOU EXPLAIN WHY THAT IS -- IF THERE'S
23 NO ACRYLAMIDE ADMINISTERED, WHY THERE ARE MICRONUCLEI.

24 A YEAH. WELL, A MOUSE PRODUCES MICRONUCLEI
25 FROM ALL SORTS OF PROCESSES. SO A NORMAL MOUSE IS GOING
26 TO CONTAIN A CERTAIN NUMBER OF MICRONUCLEI.

27 IT MIGHT REFLECT EXPOSURES FROM OTHER
28 DIETARY PRODUCTS. IT MIGHT REPRESENT GENETIC EFFECTS

1 THAT THE MICE THEMSELVES ARE RESPONSIBLE FOR. IN ANY
2 CASE, IT'S A BACKGROUND. IT'S A BACKGROUND THAT IS
3 GOING TO BE PRESENT.

4 MR. METZGER: ALL RIGHT.

5 THE COURT: LET ME ASK YOU THIS: SO WHAT DOES IT
6 MEAN, TO PRODUCE MICRONUCLEI?

7 THE WITNESS: MICRONUCLEI ARE RECOGNIZED TO BE
8 MEASURES OF MUTATION AND GENOTOXIC EFFECTS IN MICE.

9 THE COURT: AND THEN WHERE DO WE GO FROM THERE --
10 ASSUMING THESE MICRONUCLEI ARE PRODUCED, WHERE DO WE GO
11 FROM THERE TO CANCEROUS CELLS?

12 THE WITNESS: WELL, MUTATION IS A NECESSARY FIRST
13 STEP IN THE PRODUCTION OF CANCER. SO WHEN DNA HAS BEEN
14 MUTATED IN A CERTAIN WAY, IT PRODUCES A -- WELL, IT'S
15 OFTEN CALLED A HIT. AND THIS HIT CAN THEN BE PROGRESSED
16 IN SUBSEQUENT DIVISIONS OF THE CELL TO FORM A
17 MALIGNANCY.

18 THE COURT: WELL, THAT'S MY QUESTION. ARE THERE
19 STUDIES THAT TAKE THE NEXT STEP? SO WE HAVE
20 MICRONUCLEI -- AND SO IT MAY, MAY NOT? WHAT HAPPENS
21 AFTERWARDS? IS THERE ANY TESTING OR STUDIES THAT SHOW
22 THAT ACTUAL CANCER CELLS WERE PRODUCED TO RESULT IN
23 MALIGNANCY?

24 THE WITNESS: YES. WELL, THEY DIDN'T DO THAT IN
25 THESE PARTICULAR STUDIES. THEY WERE ONLY LOOKING AT THE
26 END POINT OF THE MICRONUCLEI, WHICH IS MEASURES OF
27 MUTATION OR GENOTOXIC EFFECTS.

28 THERE HAVE BEEN OTHER STUDIES THAT HAVE

1 SHOWN THAT INCREASES IN MICRONUCLEI IN ANIMALS ALSO
2 REFLECT THE INCREASED RISK OF DIFFERENT FORMS OF CANCER.

3 THE COURT: WELL, I'LL LOOK FORWARD TO HEARING
4 ABOUT THAT.

5 COUNSEL?

6 MR. METZGER: WE HAVE AN EXPERT WHO WILL TESTIFY
7 ABOUT THE EPIDEMIOLOGY OF THAT, YOUR HONOR.

8 THE COURT: AND THEN ULTIMATELY TIE IT INTO
9 ACRYLAMIDE AND COFFEE?

10 MR. METZGER: TYING IT INTO ACRYLAMIDE, I MEAN,
11 SPECIFICALLY. AS FAR AS ACRYLAMIDE IN COFFEE, THERE
12 HAVEN'T BEEN THAT MANY STUDIES DONE.

13 THE COURT: WELL, I'LL HEAR ABOUT THAT LATER.

14 Q BY MR. METZGER: ALL RIGHT. SO IF WE LOOK
15 AT THE SECOND ROW, WHERE THE ANIMALS -- THE MICE WERE
16 ADMINISTERED 1 MILLIGRAM PER KILOGRAM OF ACRYLAMIDE, THE
17 NUMBER OF MICRONUCLEI PER 1,000 CELLS WAS 1.2165;
18 CORRECT?

19 A YES.

20 MR. SCHURZ: YOUR HONOR, BY READING -- THE
21 UNDERLYING DATA AND THE UNDERLYING ARTICLE IS HEARSAY.
22 BY READING IT INTO THE RECORD, IT DOESN'T CHANGE THE
23 HEARSAY NATURE OF THE DATA.

24 THE COURT: YOU'RE RIGHT.

25 NEXT QUESTION.

26 Q BY MR. METZGER: ALL RIGHT. WELL, DR.
27 RAPPAPORT, LET'S TRY TO CUT TO THE CHASE HERE. AND
28 WOULD YOU TELL US WHAT YOU DID WITH THIS DATA, ONCE YOU

1 COMPILED IT.

2 A I WANTED TO DETERMINE WHETHER THERE WAS -- I
3 WANTED TO INVESTIGATE THE SHAPE OF THE RELATIONSHIP
4 BETWEEN THE ADMINISTERED DOSE AND THE NUMBER OF
5 MICRONUCLEATED CELLS.

6 Q WHY DID YOU WANT TO DO THAT?

7 A BECAUSE IT GETS BACK TO THIS QUESTION OF
8 WHETHER, AT LOW DOSE, A LINEAR MODEL FOR CARCINOGENICITY
9 WOULD BE CONSISTENT WITH THESE STUDIES.

10 Q ALL RIGHT. AND HOW DID YOU GO ABOUT DOING
11 THAT?

12 THE WITNESS: WITH YOUR PERMISSION, YOUR HONOR,
13 I'D LIKE TO PERHAPS WRITE FURTHER NOTATION ON THE BOARD.

14 THE COURT: OKAY.

15 THE WITNESS: IN THIS CASE, WE HAVE AN
16 ADMINISTERED DOSE. AND THE OUTCOME IN THIS CASE IS THE
17 NUMBER OF NUCLEI. AND I'M INTERESTED IN DETERMINING
18 WHAT IS THE SHAPE OF THE RELATIONSHIP BETWEEN
19 ADMINISTERED DOSE AND PRODUCTION OF MICRONUCLEI.

20 IN THIS CASE, WE KNOW THAT THERE WAS A BIG
21 BACKGROUND. SO THERE'S AN INTERCEPT THAT'S REPRESENTED
22 BY THE CONTROL ANIMALS.

23 IF A LINEAR MODEL FITS THE DATA, AS I HAD
24 SUGGESTED BEFORE, THEN WE WOULD EXPECT TO SEE THAT AS
25 THE ADMINISTERED DOSE INCREASES, THERE'S A SIMPLE LINEAR
26 RELATIONSHIP.

27 IN THIS CASE, WE WOULD HAVE WHAT ARE CALLED
28 TWO PARAMETERS FOR THE MODEL. THE FIRST WOULD BE THE

1 INTERCEPT, WHICH I'LL ABBREVIATE TO BE ZERO. AND THE
2 SECOND ONE WOULD BE THE SLOPE, STRAIGHT-LINE SLOPE,
3 WHICH I'LL CALL B1.

4 IN THIS CASE, WE COULD WRITE A SIMPLE
5 FORMULA THAT WOULD SAY THAT, UNDER THIS MODEL, THE
6 MICRONUCLEI ARE EQUAL TO B0 PLUS B1 TIMES THE
7 ADMINISTERED DOSE.

8 A SIMPLE LINEAR MODEL: IT'S AN INTERCEPT
9 AND SLOPE.

10 SO I WANTED TO INVESTIGATE WHETHER THIS
11 MODEL ADEQUATELY FIT THE DATA FROM THE TWO STUDIES:
12 EMERSON, THE STUDY THAT YOU'RE SHOWING HERE; AND ALSO,
13 THE ZEIGER STUDY.

14 I ALSO WANTED TO SEE IF THERE WAS EVIDENCE
15 OF NONLINEAR. SO I USED A SECOND MODEL, WHERE AGAIN WE
16 HAVE MICRONUCLEI. WE HAVE ADMINISTERED DOSE. WE HAVE
17 AN INTERCEPT.

18 AND I WANTED TO INVESTIGATE WHETHER THERE
19 WAS SOME EVIDENCE THAT WE STARTED TO SEE A DEVIATION
20 FROM LINEARITY. AND THE DEVIATION COULD BE EITHER
21 POSITIVE OR NEGATIVE.

22 SO IN THIS CASE, WE HAVE THREE PARAMETERS.
23 WE HAVE THE INTERCEPT TERM, THE ZERO, AS BEFORE. WE
24 HAVE SOME LINEAR PORTION, THE LOW-DOSE LINEAR PORTION,
25 WHERE WE STILL HAVE THE SLOPE, B1.

26 AND THEN AT THE HIGHER DOSE, WE WIND UP WITH
27 SOMETHING THAT'S GOING TO GIVE US CURVATURE UPWARDS OR
28 DOWNWARDS. AND MATHEMATICALLY, THAT CAN BE DONE IN

1 TERMS OF A SECOND PARAMETER, WHICH WE'LL CALL B2.

2 MATHEMATICALLY, IT LOOKS LIKE THIS:

3 MICRONUCLEI IS EQUAL TO ZERO PLUS B1 TIMES ADMINISTERED
4 DOSE, PLUS B2 TIMES THE ADMINISTERED DOSE, SQUARED. THE
5 SQUARED -- IT'S QUADRATIC; IT'S CALLED A QUADRATIC
6 TERM -- ALLOWS FOR THIS CURVATURE EITHER UPWARDS IF B2
7 IS POSITIVE, OR DOWNWARD IF B2 IS NEGATIVE.

8 SO IT'S A VERY SIMPLE AND EFFICIENT WAY OF
9 DETERMINING WHETHER THERE'S SOME EVIDENCE OF
10 NONLINEARITY AS THE DOSE GETS HIGHER.

11 I THEN INVESTIGATED A THIRD MODEL, SIMPLY
12 BECAUSE IN THE REPORT I WROTE FOR YOU, IT WAS BASED UPON
13 A CONSULTANT THAT HAD WRITTEN -- OR HAD MADE A
14 DECLARATION SAYING THAT THERE WAS A THRESHOLD FOR
15 INDUCTION OF MICRONUCLEI.

16 Q BY MR. METZGER: STOP JUST A MOMENT. DEFINE
17 A "THRESHOLD," PLEASE, FOR THE COURT.

18 A I'LL DEFINE IT HERE.

19 SO WE HAVE, AGAIN, THE MICRONUCLEI AND THE
20 ADMINISTERED DOSE. WE HAVE AN INTERCEPT, AS ALWAYS.

21 UNDER THE IDEA OF A THRESHOLD, WHICH WE'LL
22 JUST CALL T, THERE IS A DOSE, AN ADMINISTERED DOSE, OVER
23 WHICH THERE WILL BE NO ADDITIONAL PRODUCTION OF
24 MICRONUCLEI. IN OTHER WORDS, WE'LL HAVE A COMPLETELY
25 FLAT RELATIONSHIP UP TO THIS POINT OF THE THRESHOLD.

26 AND THEN UNDER THE HYPOTHESIS THAT'S BEEN
27 GENERATED BY THE OTHER EXPERT, THEN YOU WOULD HAVE A
28 LINEAR RELATIONSHIP.

1 SO HERE WE HAVE, AGAIN, A ZERO. HERE WE
2 HAVE B1 REPRESENTING THE LINEAR SLOPE. AND THEN WITH
3 THIS MODEL, MICRONUCLEI WOULD BE EQUAL TO THE ZERO PLUS
4 B1 TIMES ADMINISTERED DOSE, MINUS T.

5 SO WE SUBTRACT OFF THIS THRESHOLD MODEL TO
6 GET THE LINEAR PORTION. SO IT'S FLAT, AND THEN A LINEAR
7 RELATIONSHIP THEREAFTER.

8 SO THESE WERE THE THREE MODELS THAT I WANTED
9 TO INVESTIGATE. AND I DID THAT USING STATISTICAL TOOLS
10 THAT WE WILL DISCUSS.

11 BUT MODEL 1, MODEL 2, AND MODEL 3, THE POINT
12 IS THAT THE SIMPLE LINEAR MODEL ADEQUATELY FITS THE
13 DATA. AND UNDER THE PRINCIPLE OF PARSIMONY, WE WOULD
14 SAY WE HAVE NO EVIDENCE WITH WHICH TO ACCEPT A DIFFERENT
15 MODEL.

16 IF THERE'S STATISTICAL EVIDENCE THAT WE HAVE
17 CURVATURE UNDER MODEL 2 OR WE HAVE A THRESHOLD UNDER
18 MODEL 3, THEN WE WOULD SAY THAT THE LINEAR MODEL IS NOT
19 ADEQUATE TO REPRESENT THE DATA.

20 Q TO PUT THIS IN CONTEXT, WAS ONE OF THE
21 REASONS THAT YOU INVESTIGATED THE LINEARITY OR
22 NONLINEARITY OF THIS DATA BECAUSE CERTAIN EXPERTS HAVE
23 PROPOSED THAT THERE WAS A THRESHOLD BELOW WHICH THERE
24 WAS NO EFFECT?

25 A YES, EXACTLY.

26 MR. SCHURZ: WELL, OBJECTION. IT'S IRRELEVANT.

27 THE COURT: OVERRULED.

28 Q BY MR. METZGER: ALL RIGHT. SO LET'S --

1 LOOKING AT TABLE 1, I HAVE A QUESTION FOR YOU. I HOPE
2 THIS ISN'T HEARSAY. WE'LL SEE.

3 AT AN ADMINISTERED DOSE OF 1 MILLIGRAM PER
4 KILOGRAM, I SEE THAT THE NUMBER OF MICRONUCLEI IS
5 SLIGHTLY GREATER THAN AT 3 MILLIGRAMS PER KILOGRAM. IS
6 THAT -- AM I READING THAT CORRECTLY?

7 A YES.

8 Q OKAY. AND IS THAT OF ANY SIGNIFICANCE?

9 A IT POINTS TO THE STATISTICAL NATURE OF THE
10 PROBLEM. SEE, YOU HAVE A LARGE BACKGROUND. AT ZERO
11 DOSE, THE ANIMALS HAD 1.2 MICRONUCLEI PER 1,000 CELLS.
12 EVEN GOING UP TO 30 MILLIGRAMS PER KILOGRAM, THE ONLY --
13 WE DIDN'T EVEN DOUBLE THE BACKGROUND NUMBER.

14 SO THE STATISTICAL ISSUE IS TO DISTINGUISH
15 LOW DOSES FROM THE BACKGROUND. NOW --

16 THE COURT: AND ALSO, LET ME JUST ADD TO MR.
17 METZGER'S QUESTION: GOING FROM 6 DOSES TO 12 DOSES,
18 THERE'S ALSO A DROP.

19 MR. METZGER: NO.

20 THE COURT: DOESN'T IT GO FROM 2,297 MICRONUCLEI
21 TO 2,255?

22 Q BY MR. METZGER: EXPLAIN, DR. RAPPAPORT.

23 A I'M NOT SURE I UNDERSTAND THE QUESTION.

24 Q THE JUDGE IS REFERRING TO THAT DATA OF THE
25 NUMBER OF MICRONUCLEI, 2,297, DROPPING TO 2,255. COULD
26 YOU EXPLAIN THAT.

27 A IN PART, IT'S BECAUSE THE NUMBER OF CELLS
28 THAT WERE COUNTED IS SMALLER. THEY DIDN'T COUNT EXACTLY

1 THE SAME NUMBER OF CELLS IN EACH EXPERIMENT. AT THE 12
2 MILLIGRAMS PER KILOGRAM PER DAY, IT WAS 1,595,000. AT
3 THE 6 MILLIGRAMS PER KILOGRAM, IT WAS 1,654. SO THE
4 DENOMINATOR THAT'S USED --

5 THE COURT: ALL RIGHT. SO REALLY WHAT YOU'RE
6 TELLING ME IS THAT THE FOURTH COLUMN IS THE COLUMN WE
7 SHOULD LOOK AT?

8 THE WITNESS: YES. IT'S THE FOURTH COLUMN THAT
9 REALLY GIVES THE RESPONSE THAT'S NORMALIZED FOR THE
10 NUMBER OF CELLS THAT WERE COUNTED.

11 THE COURT: ALL RIGHT.

12 Q BY MR. METZGER: OKAY.

13 A ALL RIGHT. SO YOU SEE STATISTICAL
14 VARIATION; ESPECIALLY AT THE LOWER DOSES, BECAUSE IT'S
15 THE HARDEST TO DISTINGUISH FROM BACKGROUND. REMEMBER,
16 THERE WERE ONLY FIVE ANIMALS PER GROUP THAT WERE
17 ADMINISTERED THE ACRYLAMIDE. IT'S A RELATIVELY SMALL
18 NUMBER OF ANIMALS.

19 SO THAT THE TRUE VALUE, THE TRUE RESPONSE,
20 IS ESTIMATED BY THOSE FIVE ANIMALS. IF THEY HAD A
21 THOUSAND ANIMALS IN THIS GROUP, YOU'D HAVE A MUCH MORE
22 PRECISE ESTIMATE AND WOULDN'T SEE AS MUCH VARIATION.

23 WE'LL SEE A LITTLE BIT OF EVIDENCE OF THAT
24 WHEN WE GO TO THE ZEIGER STUDY.

25 Q OKAY. WELL, WHY DON'T WE DO THAT. IS TABLE
26 2 DATA THAT YOU COMPILED FROM THE ZEIGER STUDY?

27 A YES.

28 Q OKAY. AND TELL US A LITTLE ABOUT THE ZEIGER

1 STUDY AND HOW IT RELATED TO THE ABRAMSSON-ZETTERBERG
2 STUDY.

3 A THEY ALSO USED THE MICRONUCLEUS TEST IN
4 MICE, ONLY THIS -- IN THIS CASE, INSTEAD OF INJECTING
5 THE MICE WITH ACRYLAMIDE, THE ACRYLAMIDE WAS
6 ADMINISTERED IN THE DIET.

7 AND IN THIS CASE, THEY HAD MORE DOSE GROUPS.
8 THEY HAD MORE DOSE GROUPS IN THE LOW-DOSE REGION. YOU
9 CAN SEE THEY HAD FOUR GROUPS BETWEEN THE CONTROL GROUP
10 AND 1 MILLIGRAM PER KILOGRAM, WHICH WAS THE LOWEST DOSE
11 GROUP IN THE PREVIOUS STUDY.

12 ALL THE OTHER COLUMNS ARE CONSTRUCTED IN THE
13 SAME WAY, EXCEPT FOR THE SECOND ONE. AND THAT'S FOR
14 THIS REASON: THE NORMAL DIET THAT'S GIVEN TO MICE, THE
15 CHOW THAT'S FED TO THEM, CONTAINS SOME ACRYLAMIDE. IT'S
16 BECAUSE THE CHOW IS HEATED AT SOME POINT IN THE PROCESS
17 AND PRODUCES, VIA THIS MAILLARD REACTION, A SMALL AMOUNT
18 OF ACRYLAMIDE.

19 IN THIS STUDY, THE ZEIGER STUDY, BECAUSE
20 THEY HAD MEASURED ADDUCTS OF ACRYLAMIDE, EVEN IN THE
21 CONTROL ANIMALS, I WAS ABLE TO ESTIMATE THE AMOUNT OF
22 EXPOSURE TO ACRYLAMIDE THAT THOSE ANIMALS, CONTROL
23 ANIMALS, HAD RECEIVED FROM THE DIET. AND THAT TURNED
24 OUT TO BE .0433 MILLIGRAMS PER KILOGRAM PER DAY.

25 SO THEN I WAS ABLE TO ADJUST ALL THE DATA TO
26 REFLECT NOT ONLY THE ACRYLAMIDE THAT THEY RECEIVED FROM
27 THE ADMINISTRATION IN THE DRINKING WATER, BUT ALSO THE
28 ACRYLAMIDE THAT HAD BEEN RECEIVED FROM THE DIET THAT THE

1 ANIMALS WERE EATING.

2 Q AND WHY DID YOU DO THAT ADJUSTMENT?

3 A JUST TO PROVIDE A MORE PRECISE ESTIMATE OF
4 THE RESPONSE.

5 MR. METZGER: OKAY.

6 THE COURT: DO YOU THINK THAT THESE STUDIES WITH
7 THE FIVE MICE PER DOSE, OR TEN MICE, IS SUFFICIENT TO
8 DETERMINE VALID CONCLUSIONS?

9 THE WITNESS: I THINK IT IS, IF WE LOOK AT THE
10 TOTALITY OF THE DATA, YOUR HONOR. AND I'LL DO THAT IN A
11 MOMENT. I WOULD THINK THAT IF WE REALLY WANTED MORE
12 CERTAINTY ABOUT EACH DOSE LEVEL, IT WOULD BE BETTER TO
13 USE MORE ANIMALS. AND THE MORE YOU HAVE, THE CLOSER YOU
14 ARE TO TRUTH. BUT EVEN --

15 THE COURT: AND THERE'S A DIFFERENCE IF YOU STUDY
16 THE DIETS OF TEN FOOTBALL PLAYERS COMPARED TO TEN
17 GYMNASTS.

18 THE WITNESS: YES, YOUR HONOR.

19 THE COURT: OKAY.

20 THE WITNESS: IT WOULD BE BETTER TO LOOK AT A
21 THOUSAND FOOTBALL PLAYERS AND A THOUSAND GYMNASTS.

22 Q BY MR. METZGER: ALL RIGHT. WELL, DR.
23 RAPPAPORT, GENERALLY, WHAT DID THIS DATA SUGGEST TO YOU
24 THAT YOU THEN WANTED TO TEST WITH YOUR STATISTICAL
25 ANALYSES?

26 A AS SHOWN HERE, I WANTED TO TEST THESE THREE
27 DIFFERENT MODELS. I APPLIED THESE MODELS TO BOTH OF THE
28 DATA SETS, TO SEE WHETHER A LINEAR RELATIONSHIP

1 ADEQUATELY DESCRIBED THE DATA.

2 Q OKAY.

3 A I THINK, IF WE GO ON TO LOOK AT THE FIGURES,
4 WE'LL SEE --

5 Q ALL RIGHT. WELL, LET'S GO ON TO THE NEXT
6 SLIDE, WHICH HAS TABLE 3 THAT YOU'VE PREPARED.

7 A YES. AND THIS IS A COMPLICATED TABLE. AND
8 I'LL BRIEFLY SUMMARIZE THE IMPORTANT POINTS.

9 YOU SEE THAT THERE ARE THE TWO STUDIES. THE
10 STUDY SHOWN FIRST WAS THE ABRAMSSON-ZETTERBERG STUDY,
11 AND THEN THE ONE BELOW IS THE ZEIGER STUDY.

12 IN EACH CASE, YOU SEE SOMETHING CALLED
13 "MODEL" IN THE SECOND COLUMN. THAT REPRESENTS THESE
14 THREE MODELS THAT I'VE SHOWN HERE: THE SIMPLE LINEAR
15 MODEL; THE LINEAR QUADRATIC MODEL, WHICH WOULD SHOW
16 CURVATURE; AND THE THRESHOLD MODEL.

17 AND THEN THERE ARE THE ESTIMATES OF THE
18 PARAMETERS: B_0 , B_1 , AND B_2 ; WHICH, AGAIN, I HAVE SHOWN
19 HERE ON MY FIGURES.

20 THEN THERE'S A COLUMN CALLED "R SQUARED,"
21 WHICH IS A MEASURE OF THE GOODNESS OF FIT OF EACH MODEL.
22 R SQUARED WOULD BE BETWEEN ZERO AND 1. THE CLOSER IT
23 GETS TO 1, THE BETTER THE FIT OF THE MODEL.

24 Q LET ME INTERRUPT YOU.

25 YOU SAY "GOODNESS OF FIT OF MODEL." COULD
26 YOU TELL US WHAT THAT'S ABOUT. WHAT DOES THAT MEAN?

27 A IN EACH CASE, YOU'RE LOOKING FOR THE
28 EVIDENCE FAVORING A PARTICULAR MODEL. AND ONE FORM OF

1 EVIDENCE THAT STATISTICIANS USE IS CALLED "GOODNESS OF
2 FIT," AND IT'S OFTEN GIVEN IN TERMS OF WHAT'S CALLED "R
3 SQUARED."

4 Q IS THAT A -- "COEFFICIENT OF VARIATION," IS
5 THAT WHAT THAT'S CALLED?

6 A YES. R SQUARED IS ALSO CALLED THE
7 "COEFFICIENT OF VARIATION."

8 Q OKAY. AND THAT'S ONE MODEL TO ASSESS
9 GOODNESS OF FIT TO DATA; IS THAT --

10 A THAT'S CORRECT. AND YOU CAN SEE FOR THE R
11 SQUARED VALUES FROM MODEL 1, IT'S .9803; IN 2, IT'S
12 .9824; IN 3, .9457, AND SO ON. SO IT GIVES YOU SOME
13 IDEA OF THE GOODNESS OF FIT BY THAT MEASURE.

14 BUT R SQUARED IS A RATHER UNDISCRIMINATING
15 MEASURE. IT DOESN'T TELL YOU ANYTHING ABOUT THE WEIGHT
16 OF EVIDENCE SUPPORTING EACH PARTICULAR MODEL. IT JUST
17 GIVES YOU SOME MEASURE OF THE OVERALL GOODNESS OF FIT.

18 AND TO GET A BETTER IDEA OF THE EVIDENCE
19 THAT WOULD SUPPORT EACH MODEL, I USED ANOTHER METRIC
20 THAT'S CALLED AIC.

21 Q WHAT DOES THAT STAND FOR?

22 A IT STANDS FOR AKAIKE'S INFORMATION
23 CRITERION.

24 Q OKAY.

25 A IT'S WIDELY USED IN SOME BRANCHES OF
26 STATISTICS WHERE YOU WANT TO FIND THE EVIDENCE
27 SUPPORTING A PARTICULAR MODEL, THE ACTUAL WEIGHT OF
28 EVIDENCE. AND IN A PROCEEDING LIKE THIS, WHERE WEIGHT

1 OF EVIDENCE IS IMPORTANT, IT SEEMED LIKE THIS WAS A VERY
2 VALID WAY OF TRYING TO MAKE THAT POINT.

3 SO I USED AIC AND DID SOME MANIPULATIONS
4 WITH AIC, AND IT ALLOWED ME TO COMPARE THE FITS OF EACH
5 MODEL AND COMPARE THEM TO EACH OTHER.

6 Q WHEN YOU SAY YOU DID "SOME MANIPULATIONS OF
7 AIC," WHAT DO YOU MEAN?

8 A WELL, AIC NEEDS TO BE ADJUSTED FOR THE
9 NUMBER OF PARAMETERS IN THE MODEL.

10 IF YOU HAVE SMALL AMOUNTS OF DATA, AS WE DO
11 HERE -- SO WE ONLY HAD A FEW DOSE GROUPS IN EACH CASE.
12 IF YOU HAVE MORE PARAMETERS IN THE MODEL, YOU'RE ALWAYS
13 GOING TO GET A BETTER -- IT'S GOING TO BE A BETTER
14 MEASURE OF THE FIT BECAUSE YOU'RE GIVEN MORE
15 OPPORTUNITIES TO MANIPULATE THE SHAPE OF THE
16 RELATIONSHIP WITH THOSE PARAMETERS.

17 BUT IF YOU ADJUST FOR THE NUMBER OF
18 PARAMETERS -- THAT IS, IF YOU HAVE THREE PARAMETERS, YOU
19 HAVE TO BE MORE CONSERVATIVE -- THEN YOU GET A METRIC
20 CALLED AICC, WHICH IS THE AIC VALUE THAT'S BEEN ADJUSTED
21 FOR PARAMETERS. AND THAT'S A BETTER MEASURE TO USE FOR
22 COMPARISON OF MODELS WITH SMALL AMOUNTS OF DATA.

23 Q IS AICC -- ARE ALL OF THESE MODELS -- THE R
24 SQUARED AND THE AIC AND AICC, ARE THEY ALL MODELS THAT
25 HAVE BEEN GENERALLY ACCEPTED IN THE STATISTICAL
26 COMMUNITY FOR ASSESSING GOODNESS OF FIT OF MODELS?

27 A OH, YES, YES. VERY WIDELY USED.

28 Q OKAY.

1 A IN FACT, THEY'RE USUALLY DEFAULT OUTPUTS IN
2 STATISTICAL PACKAGES THAT DO THESE KINDS OF ANALYSES.

3 Q ALL RIGHT. PLEASE PROCEED AND TELL US WHAT
4 YOU FOUND.

5 A ALL RIGHT. WELL, THE SMALLER THE AICC, THE
6 BETTER THE MODEL, THE BETTER THE FIT OF THE MODEL. AND
7 AS YOU'LL SEE, IN BOTH CASES, THE SMALLEST AICC VALUE
8 WAS GIVEN BY MODEL 1, WHICH IS THE SIMPLE LINEAR MODEL.

9 AND THEN WE CAN ACTUALLY COMPARE --

10 Q HOLD IT. WHERE IS THAT, WHEN YOU'RE
11 COMPARING MODEL 1 VERSUS MODEL 2, AND WHAT NUMBER ARE
12 YOU LOOKING AT THAT SHOWS THAT --

13 A OKAY. IF YOU LOOK AT AICC --

14 Q YES.

15 A -- AND YOU SEE FOR MODEL 1, IN THE
16 ABRAMSSON-ZETTERBERG STUDY, IT WAS MINUS 39.285.

17 Q YES.

18 A AND THEN FOR MODEL 2, IT WAS MINUS 33.088;
19 CORRECT?

20 Q YEAH.

21 A AND MINUS 39 IS SMALLER THAN MINUS 38.

22 Q OKAY.

23 A BECAUSE THEY'RE NEGATIVE NUMBERS, THE MORE
24 NEGATIVE, THE SMALLER THE NUMBER IS.

25 Q SO FOR THE AICC PARAMETER -- OR MODEL, THE
26 LOWER THE NUMBER, THE BETTER THE FIT? IS THAT HOW IT
27 WORKS?

28 A THE SMALLER THE NUMBER, THE BETTER THE FIT.

1 Q GOT IT. GO AHEAD.

2 A SO NOW WE CAN COMPARE MODEL 1 VERSUS MODEL
3 2. SO THIS WOULD BE THE SIMPLE LINEAR MODEL, 1; OR THE
4 LINEAR QUADRATIC MODEL, ALLOWING CURVATURE, IN MODEL 2.

5 AND IN THE -- IN THIS MODEL 1 VERSUS MODEL 2
6 COMPARISON, YOU CAN SEE THAT THERE WAS A FAIRLY
7 SUBSTANTIAL DIFFERENCE IN THE ICC VALUES, FAVORING MODEL
8 1.

9 AND ONE NICE FEATURE OF USE OF AICC IS IT
10 GIVES US THE EVIDENCE SUPPORTING THE USE OF THAT MODEL.
11 AND IN THIS CASE, THE ABRAMSSON-ZETTERBERG STUDY, THE
12 EVIDENCE WAS 22.2 TIMES STRONGER SUPPORTING MODEL 1 THAN
13 MODEL 2. AND IN THE ZEIGER STUDY, IT WAS 3.75, OR ABOUT
14 FOUR TIMES STRONGER.

15 SO IN BOTH CASES, IT'S A SUBSTANTIAL
16 IMPROVEMENT IN THE EVIDENCE SUPPORTING A SIMPLE LINEAR
17 MODEL OVER THE LINEAR QUADRATIC MODEL.

18 AND IF WE GO TO THE LAST SET OF
19 CALCULATIONS, WHERE WE COMPARE MODEL 1 WITH THE
20 THRESHOLD MODEL, 3, WE SEE EVEN STRONGER EVIDENCE
21 SUPPORTING THE SIMPLE LINEAR MODEL, 1.

22 FOR THE FIRST STUDY, ABRAMSSON-ZETTERBERG,
23 34 TIMES STRONGER EVIDENCE. AND IN THE ZEIGER STUDY --
24 MORE ANIMALS -- 873,000 TIMES STRONGER EVIDENCE.

25 SO THOSE DATA WOULD SHOW VERY CLEARLY THAT
26 MODEL 3, WHICH ASSUMED A THRESHOLD OF 6 MILLIGRAMS PER
27 KILOGRAM -- WHICH IS WHAT THE PRIOR EXPERT HAD
28 SUGGESTED -- DID NOT FIT THE DATA NEARLY AS WELL AS A

1 SIMPLE LINEAR MODEL.

2 AND EVEN A MODEL THAT ALLOWS FOR SOME
3 CURVATURE AT HIGHER DOSES DID NOT FIT THE DATA -- EITHER
4 DATASET AS WELL AS A SIMPLE LINEAR MODEL.

5 Q ALL RIGHT. AND HAVE YOU SHOWN THIS ALSO
6 GRAPHICALLY?

7 A YES.

8 Q WHY DON'T WE TURN TO THE NEXT SLIDE.

9 AND THIS IS FIGURE 1 FROM YOUR REPORT; IS
10 THAT CORRECT?

11 A YES.

12 Q EXPLAIN TO HIS HONOR, IF YOU WOULD, WHAT
13 THIS SHOWS.

14 A YEAH. THESE SHOW THE FIT OF THE DATA TO THE
15 SIMPLE LINEAR MODEL, 1, FROM THE ABRAMSSON-ZETTERBERG
16 STUDY. YOU CAN SEE ALL OF THE DATA POINTS ARE SHOWN
17 WITH LITTLE CIRCLES. THE LINE REPRESENTS THE BEST FIT
18 OF THE REGRESSION, THE SIMPLE LINEAR REGRESSION. YOU
19 CAN SEE THE INTERCEPT THERE.

20 Q HOLD IT. DEFINE THAT. WHAT'S "SIMPLE
21 LINEAR REGRESSION"?

22 A SIMPLE LINEAR MODEL, NO. 1, THAT THE
23 MICRONUCLEI IS EQUAL TO THE INTERCEPT, B_0 , PLUS THE
24 SLOPE, B_1 , TIMES THE ADMINISTERED DOSE, WHICH IS SHOWN
25 ON THE AXIS.

26 SO WE HAVE -- IT'S REALLY A REPRESENTATION
27 OF WHAT I SHOWED HERE IN MY HANDWRITTEN DRAWING. YOU
28 CAN SEE -- I MEAN, I DON'T THINK YOU HAVE TO BE A

1 STATISTICIAN TO LOOK AT THOSE DATA POINTS AND SAY THE
2 DATA SEEM TO FIT THE STRAIGHT-LINE MODEL, OR THE
3 STRAIGHT-LINE MODEL SEEMS TO FIT THE DATA PRETTY WELL.

4 Q BUT YOU ACTUALLY DID THE STATISTICS WHICH
5 SHOW THAT SCIENTIFICALLY?

6 A YES. BUT IF THE STATISTICS ARE TELLING YOU
7 SOMETHING THAT YOUR BRAIN CAN'T RECOGNIZE AS BEING REAL,
8 THEN YOU HAVE TO WONDER ABOUT THE STATISTICS. SO YOU
9 ALWAYS WANT TO SEE THE EVIDENCE, FROM YOUR EYES, THAT
10 THE STATISTICS ARE MAKING SENSE. AND THIS IS A VERY
11 CLEAR EXAMPLE OF THAT.

12 THE COURT: AM I CORRECT IN ASSUMING FROM THIS
13 GRAPH AND YOUR TESTIMONY THAT THE PRODUCTION OF
14 MICRONUCLEI OCCURS NATURALLY, WITHOUT THE ADMINISTRATION
15 OF ANY DOSAGE?

16 THE WITNESS: YES. AND THAT'S GIVEN BY THE
17 INTERCEPT, WHICH IS RIGHT AT ABOUT 1.2, WHERE IT --

18 THE COURT: ALL RIGHT.

19 THE WITNESS: -- WHERE IT CROSSES THE Y AXIS.

20 THE COURT: THANK YOU.

21 AT THIS TIME WE'RE GOING TO INTERRUPT THE
22 TESTIMONY AND TAKE A 15-MINUTE RECESS SO I CAN ADDRESS
23 SOME OTHER CASES.

24 (RECESS.)

25 THE COURT: BACK ON THE RECORD IN CERT VS.
26 STARBUCKS. PROFESSOR RAPPAPORT WAS ON THE STAND. ALL
27 COUNSEL ARE PRESENT.

28 THE CLERK: SIR, YOU'VE PREVIOUSLY BEEN SWORN, AND

1 YOU'RE STILL UNDER OATH. WOULD YOU RESTATE YOUR NAME
2 FOR THE RECORD.

3 THE WITNESS: STEPHEN RAPPAPORT.

4 THE COURT: COUNSEL, YOU MAY PROCEED. MR.
5 METZGER, PLEASE.

6 MR. METZGER: THANK YOU, YOUR HONOR.

7 Q DR. RAPPAPORT, DID YOU ALSO DEVELOP A GRAPH
8 THAT ASSESSED VISUALLY THE POSSIBLE THRESHOLD MODEL?

9 A I DID.

10 Q AND IS THAT THE NEXT ONE, WHICH IS FIGURE 3
11 IN YOUR REPORT?

12 A YES.

13 Q ALL RIGHT. WHY DON'T YOU TELL US WHAT YOU
14 DID HERE.

15 A WELL, AGAIN, THESE ARE THE DATA FROM THE
16 ABRAMSSON-ZETTERBERG STUDY. THE LINEAR MODEL IS SHOWN
17 WITH A DARK BLACK LINE. YOU CAN SEE THE INDIVIDUAL DATA
18 POINTS SHOWN WITH THE DOTS.

19 THE RED LINE REPRESENTS A THRESHOLD MODEL,
20 WHICH WOULD BE MODEL 3 IN MY ANALYSIS, WHICH ASSUMES
21 THAT THE LEVEL OF MICRONUCLEI -- OR THE NUMBER OF
22 MICRONUCLEI PER 1,000 CELLS WOULD BE CONSTANT FOR ALL
23 DOSE GROUPS BELOW 6 MILLIGRAMS PER KILOGRAM.

24 AND YOU CAN SEE VISUALLY THAT THAT THRESHOLD
25 MODEL DID NOT FIT THE DATA WELL AT ALL, WHICH REINFORCES
26 THE STATISTICAL TESTS THAT WERE DONE TO EVALUATE THE
27 GOODNESS OF FIT.

28 Q OKAY. AND DID YOU ALSO ASSESS THE POSSIBLE

1 THRESHOLD MODEL FOR THE ZEIGER DATA?

2 A YES.

3 Q AND IS THAT FIGURE 4?

4 A IT IS.

5 Q ALL RIGHT. AND WHAT DID YOU FIND?

6 A ESSENTIALLY, THE SAME. YOU SEE THE FIT OF
7 THE LINEAR MODEL SEEMS QUITE GOOD. AND THE SHAPE OF THE
8 THRESHOLD MODEL, ASSUMING A THRESHOLD OF 6 MILLIGRAMS
9 PER KILOGRAM, DID NOT FIT THE DATA WELL.

10 Q OKAY. DR. RAPPAPORT, BASED UPON YOUR
11 ANALYSES OF STATISTICAL GOODNESS OF FIT OF THE THREE
12 DIFFERENT PROPOSED MODELS, WHAT DID YOU CONCLUDE
13 REGARDING THE TOXICOKINETICS OF ACRYLAMIDE?

14 A BECAUSE THERE'S NO EVIDENCE TO SUGGEST THAT
15 THE SIMPLE LINEAR MODEL WAS NOT APPROPRIATE, IT
16 REINFORCES THE IDEA THAT THE TOXICOKINETIC PROCESSES
17 RELATING PRIMARILY TO METABOLISM OF GLYCIDAMIDE REMAINED
18 LINEAR; AND ESPECIALLY IN THE LOW-DOSE REGION, WHICH IS
19 THE REGION OF RELEVANCE TO HUMANS.

20 Q WHEN YOU SAY IT REINFORCES THAT IDEA, IS
21 THAT AN OPINION THAT YOU HOLD TO A REASONABLE DEGREE OF
22 SCIENTIFIC PROBABILITY?

23 A YES.

24 Q WHAT IS THE SIGNIFICANCE OF YOUR ANALYSIS OF
25 THE TOXICOKINETICS OF ACRYLAMIDE TO ASSESSMENT OF THE
26 CARCINOGENICITY OF ACRYLAMIDE TO HUMANS?

27 A IT SUGGESTS -- WELL, IT INDICATES THAT THERE
28 WOULD BE NO REASON NOT TO ASSUME A LOW-DOSE LINEAR MODEL

1 WITH NO THRESHOLD.

2 Q OKAY. DR. RAPPAPORT, IN MODELING THE ANIMAL
3 DATA IN YOUR ANALYSES, DID YOU MAKE ANY ASSUMPTIONS
4 ABOUT THE BIOLOGICAL EFFECTS OF ACRYLAMIDE?

5 A NO, I DID NOT.

6 Q DID YOU MAKE ANY ASSUMPTIONS ABOUT THE
7 BIOLOGY OF COFFEE?

8 A NO.

9 Q DO ANY PROBLEMS ARISE FROM INTRODUCING
10 BIOLOGY INTO THE MODELING OF ANIMAL DATA TO ESTIMATE
11 HUMAN EFFECTS?

12 A IT CAN. IT CAN GENERATE PROBLEMS.

13 Q HOW SO?

14 A IF ONE HAS A SET OF DATA -- SUCH AS THOSE
15 THAT I'VE SHOWN HERE FROM THE TWO STUDIES OF THE
16 MICRONUCLEI OF MICE -- AND ONE LOOKS AT THE TOTALITY OF
17 THE DATA, IT'S VERY CLEAR FROM MY ANALYSES THAT A LINEAR
18 MODEL IS APPROPRIATE.

19 IF I HAD GONE INTO THIS EXERCISE ASSUMING
20 THAT THERE WAS A THRESHOLD, I COULD HAVE INTRODUCED BIAS
21 INTO MY ANALYSIS THAT WOULD HAVE SKEWED MY ABILITY TO
22 SEE THE UNDERLYING RELATIONSHIP.

23 I THINK THERE IS A PLACE FOR BIOLOGY IN
24 LOOKING AT DOSE-RESPONSE RELATIONSHIPS, BUT I THINK THEY
25 SHOULD COME LATER RATHER THAN BEFORE.

26 AND "LATER," IN THE SENSE THAT ONCE ONE HAS
27 ESTABLISHED WHAT THE SHAPE OF THE RELATIONSHIP LOOKS
28 LIKE, TO FIND BIOLOGICAL DATA THAT WOULD DETERMINE WHAT

1 THE MECHANISM OF ACTION WOULD BE.

2 Q ALL RIGHT. IS IT YOUR OPINION THAT THE
3 SELECTION OF A MODEL FOR PURPOSES OF RISK ASSESSMENT IS
4 ESSENTIALLY A STATISTICAL PROCESS?

5 A I WOULDN'T SAY IT'S ESSENTIALLY A
6 STATISTICAL PROCESS BECAUSE ONE HAS TO EVALUATE THE
7 QUALITY OF DATA THAT ARE USED FOR DOING THE STATISTICAL
8 ANALYSES. IT'S GARBAGE IN, GARBAGE OUT.

9 SO IF YOU HAVE GOOD DATA, THE SCIENTISTS
10 HAVE EVALUATED THE PROTOCOLS THAT WERE USED, THEY ARE --
11 HAVE PROPER SCIENTIFIC CONDUCT, THEN YES, I THINK IT IS
12 PRIMARILY A STATISTICAL EXERCISE.

13 Q AND DO YOU CONSIDER THE DATA FROM THE
14 ABRAMSSON-ZETTERBERG STUDY AND THE ZEIGER STUDY TO BE
15 GOOD-QUALITY STUDY?

16 A YES. PARTICULARLY THE ZEIGER STUDY, BECAUSE
17 THEY USED A LARGER NUMBER OF ANIMALS, THEY COUNTED MORE
18 CELLS, THEY HAD A WIDER NUMBER OF DOSE GROUPS, ET
19 CETERA.

20 Q OKAY. ARE YOU FAMILIAR WITH THE 2005 EPA
21 GUIDELINES FOR CARCINOGEN RISK ASSESSMENT?

22 A I HAVE READ THEM.

23 Q WHAT IS YOUR UNDERSTANDING OF WHAT THOSE
24 GUIDELINES RECOMMEND REGARDING THE USE OF BIOLOGY IN
25 MODELING HUMAN CANCER RISK?

26 A I THINK THEY GIVE SOMEWHAT MORE CREDENCE TO
27 THE USE OF BIOLOGY THAN I DO.

28 Q DO YOU AGREE WITH THE EPA'S GUIDELINES

1 RECOMMENDING THE USE OF BIOLOGY IN MODELING HUMAN CANCER
2 RISK?

3 A NO, NOT FOR THE INITIAL EVALUATION OF THE
4 DOSE-RESPONSE RELATIONSHIPS.

5 Q WHY NOT?

6 A FOR THE REASONS I'VE JUST MENTIONED, I THINK
7 ONCE YOU START OVERRIDING THE ANALYSES OF THE DATA BY
8 YOUR PRECONCEIVED NOTIONS ABOUT BIOLOGY, YOU CAN
9 INTRODUCE BIASES INTO THE PROCESS.

10 Q HAVE YOU FORMED AN OPINION AS TO WHETHER
11 SIMPLE OR COMPLEX MODELS ARE PREFERABLE FOR ASSESSING
12 HUMAN CANCER RISK?

13 A THE SIMPLEST MODEL THAT EXPLAINS THE DATA
14 ADEQUATELY IS THE MODEL THAT SHOULD BE USED.

15 Q WHY?

16 A IT'S THIS PRINCIPLE OF PARSIMONY. IT'S
17 BASICALLY AN ACCEPTED PRINCIPLE IN SCIENCE: THAT YOU
18 DON'T NEED TO INTRODUCE COMPLEXITY WHEN YOU HAVE A MODEL
19 THAT WORKS WELL.

20 Q HAVE YOU FORMED AN OPINION AS TO WHETHER THE
21 TOXICOKINETIC PROCESSES FOR ACRYLAMIDE ARE LINEAR IN THE
22 LOW-DOSE RANGE?

23 A YES. THERE'S NO EVIDENCE THAT I'VE BEEN
24 ABLE TO FIND FROM ANY OF THE REFERENCES THAT I'VE
25 REVIEWED OR MY OWN ANALYSES TO SUGGEST THAT THERE ARE
26 NONLINEAR TOXICOKINETIC PROCESSES AT LOW DOSES IN
27 HUMANS.

28 Q AND IS THE LOW-DOSE RANGE RELEVANT TO HUMAN

1 CANCER RISK?

2 A YES, OF COURSE.

3 Q WHY?

4 A BECAUSE PEOPLE ARE EXPOSED TO LOW LEVELS OF
5 ACRYLAMIDE FROM DIETARY SOURCES.

6 Q AND HAVE YOU FORMED AN OPINION TO A
7 REASONABLE DEGREE OF SCIENTIFIC PROBABILITY THAT A
8 LINEAR MODEL WOULD BE APPROPRIATE FOR DESCRIBING THE
9 TOXICOKINETICS OF ACRYLAMIDE?

10 A YES. BASED UPON THE EVIDENCE THAT I'VE BEEN
11 ABLE TO REVIEW, I WOULD MAKE THAT CONCLUSION.

12 Q OKAY. HAVE YOU FORMED AN OPINION AS TO
13 WHETHER A LINEAR MODEL WOULD BE APPROPRIATE FOR
14 DESCRIBING DOSE-RESPONSE RELATIONSHIPS OF HUMAN CANCER
15 RISK FROM ACRYLAMIDE?

16 A YES, I WOULD HAVE THAT OPINION.

17 Q AND WHY? WHAT'S THE BASIS FOR THAT OPINION?

18 A IT, AGAIN, RELATES TO THE LACK OF EVIDENCE
19 SUGGESTING ANY SORT OF NONLINEARITY OF THE PROCESS,
20 PRIMARILY IN THE CONVERSION OF ACRYLAMIDE TO THE
21 GENOTOXIC CARCINOGEN GLYCIDAMIDE FOLLOWING THE INGESTION
22 OF FOODS THAT CONTAIN ACRYLAMIDE.

23 Q AND WOULD YOU TELL THE COURT, WHAT IS THE
24 SIGNIFICANCE OF YOUR OPINION THAT MOST OF THE
25 TOXICOKINETIC PROCESSES OF ACRYLAMIDE APPEAR TO BE
26 LINEAR IN THE LOW-DOSE RANGE?

27 A IT WOULD JUSTIFY A RISK ASSESSMENT WHICH
28 ASSUMES LOW-DOSE LINEARITY IN DETERMINING HUMAN RISK OR

1 IN ESTIMATING HUMAN RISK FROM EXPOSURE TO LOW LEVELS OF
2 ACRYLAMIDE.

3 Q ALL RIGHT. MAY WE CHANGE TOPICS?

4 A YES.

5 Q OKAY. ONE OF THE OTHER THINGS THAT I ASKED
6 YOU TO DO IN THIS CASE WAS TO EVALUATE DR. BARBARA
7 PETERSEN'S ASSESSMENT OF THE CONSUMPTION OF COFFEE BY
8 THE UNITED STATES POPULATION; CORRECT?

9 A YES.

10 Q ALL RIGHT. AND COULD YOU TELL US,
11 GENERALLY, WHAT YOU CONCLUDED.

12 A YES. I READ DR. PETERSEN'S DEPOSITIONS, AND
13 I HAD DIFFICULTY FOLLOWING HER REASONING. SO I LOOKED
14 AT THE WORDING OF THE REGULATION THAT WAS DEVELOPED
15 UNDER PROP 65 FOR EVALUATING CARCINOGENIC RISKS IN
16 HUMANS.

17 AND I THINK THE WORDING IS ON ONE OF THE
18 SLIDES, PERHAPS.

19 Q NEXT SLIDE.

20 ARE YOU REFERRING TO TITLE 27 OF THE
21 CALIFORNIA CODE OF REGULATIONS, SECTION 25721?

22 A YES. AND THERE'S THIS QUOTATION THAT
23 INDICATES WHAT THE STATE OF CALIFORNIA USES TO DETERMINE
24 RISKS OF EXPOSURE TO CANCER-CAUSING SUBSTANCES IN
25 CONSUMER PRODUCTS. AND THEY SAY, QUOTE:

26 "BY USING THE AVERAGE RATE OF INTAKE OR
27 EXPOSURE FOR AVERAGE USERS OF THE CONSUMER
28 PRODUCT AND NOT ON A PER CAPITA BASIS FOR THE

1 GENERAL POPULATION."

2 Q AND IS THAT STRAIGHT FROM THE REGULATION?

3 A STRAIGHT FROM THE REGULATION.

4 Q OKAY.

5 A AND DR. PETERSEN'S ANALYSIS, IN MY OPINION,
6 WAS FLAWED IN TWO WAYS.

7 FIRST, SHE DID NOT REALLY CONSIDER THE
8 AVERAGE CONSUMER. IT WAS CLEAR FROM HER ANALYSIS THAT
9 SHE HAD INCLUDED IN HER ESTIMATES PEOPLE WHO WERE NOT
10 AVERAGE CONSUMERS OF COFFEE. IN SOME CASES, IT APPEARS
11 THERE WERE CHILDREN, WHO DRANK NO COFFEE AT ALL.

12 AND SECOND, SHE DID NOT ESTIMATE THE AVERAGE
13 EXPOSURE IN THE SENSE THAT IT SHOULD HAVE BEEN
14 ESTIMATED. SHE ACTUALLY WAS TRYING TO ESTIMATE THE
15 TYPICAL EXPOSURE, WHICH IS DIFFERENT FROM THE AVERAGE
16 EXPOSURE, FOR STATISTICAL REASONS THAT I CAN DISCUSS.

17 Q WELL, LET ME ASK YOU: HOW IS IT THAT THE
18 TYPICAL EXPOSURE DIFFERS FROM AVERAGE EXPOSURE?

19 A WELL, WOULD IT BE POSSIBLE FOR ME TO MAKE
20 ANOTHER SIMPLE DRAWING?

21 Q SURE.

22 THE WITNESS: YOUR HONOR?

23 THE COURT: YES.

24 THE WITNESS: I'LL ERASE THIS ONE.

25 Q BY MR. METZGER: SURE. OR YOU MIGHT WANT TO
26 USE THE OTHER BOARD.

27 A IF WE TAKE CONSUMPTION OF COFFEE AND GO
28 FROM, SAY -- FROM ZERO TO TEN CUPS PER DAY, THEN WE TAKE

1 THE PERCENT OF CONSUMERS THAT CONSUME THAT MUCH
2 COFFEE -- I MEAN, A GIVEN AMOUNT OF COFFEE, WE SEE A
3 DISTRIBUTION. FROM MY ANALYSIS, IT LOOKS SOMETHING LIKE
4 THIS.

5 SO IT'S -- IN STATISTICAL PARLANCE, THEY
6 CALL THIS A "SKEWED" DISTRIBUTION. IT'S SKEWED TOWARDS,
7 IN THIS CASE, THE LARGER NUMBERS OF CUPS PER DAY THAT
8 ARE CONSUMED.

9 IN A SKEWED DISTRIBUTION, THE MEAN VALUE,
10 WHICH IS EQUIVALENT TO THE AVERAGE VALUE -- WHICH WOULD
11 BE GIVEN, IN THIS CASE, HERE (INDICATING) -- IS LARGER
12 THAN THE MEDIAN VALUE, WHICH IN THIS CASE WOULD BE HERE
13 (INDICATING).

14 NOW, THE MEDIAN, THAT'S THE VALUE THAT
15 REPRESENTS 50 PERCENT OF THE POPULATION. SO HALF THE
16 PEOPLE WOULD DRINK MORE COFFEE; HALF THE PEOPLE WOULD
17 DRINK LESS COFFEE. THIS WOULD BE TYPICAL.

18 THE MEAN VALUE, WHICH IS THE AVERAGE, IS
19 HIGHER THAN THE MEDIAN OR THE TYPICAL VALUE WHEN YOU
20 HAVE A SKEWED DISTRIBUTION.

21 Q HIGHER, GOING HORIZONTALLY, THOUGH, YOU
22 MEAN?

23 A YEAH. THERE WOULD BE MORE COFFEE CONSUMED
24 BY THE AVERAGE CONSUMER -- I MEAN, THE AVERAGE CONSUMER
25 WOULD CONSUME MORE COFFEE THAN THE TYPICAL CONSUMER,
26 OKAY? SO THAT'S THE DIFFERENCE.

27 AND DR. PETERSEN FOCUSED ON TYPICAL; BUT IN
28 MY READING OF THE REGULATION, THEY'RE TRYING TO EXCLUDE

1 THAT POSSIBILITY. BECAUSE SOME PEOPLE DRINK VERY LARGE
2 AMOUNTS OF COFFEE. BECAUSE ACRYLAMIDE IS IN THE COFFEE,
3 THESE PEOPLE WOULD BE AT THE GREATEST RISK.

4 AND THE AVERAGE TAKES THAT INTO ACCOUNT, TO
5 A CERTAIN EXTENT, BY GIVING A LARGER ESTIMATE OF THE
6 EXPOSURE THAN THE MEDIAN VALUE, TYPICAL.

7 MR. SCHURZ: YOUR HONOR, WE'D MOVE TO STRIKE AS
8 OFFERING A LEGAL OPINION. WHAT DR. RAPPAPORT HAS JUST
9 OFFERED IS BASED UPON HIS READING OF THE REGULATION,
10 WHICH WE'LL FIND OUT WHEN HE DID THAT.

11 HE CONSTRUES THE TERM "AVERAGE." THAT'S A
12 JOB FOR THIS COURT, NOT FOR AN EXPERT WHO IS SKILLED IN
13 THE ART OF STATISTICS.

14 THE COURT: ALL RIGHT. THANK YOU.

15 OBJECTION IS OVERRULED.

16 Q BY MR. METZGER: DR. RAPPAPORT, WHY DO YOU
17 CONCLUDE THAT DR. PETERSEN'S ANALYSIS WAS OF TYPICAL
18 CONSUMPTION RATHER THAN AVERAGE CONSUMPTION?

19 A OH, SHE STATES THAT REPEATEDLY IN HER
20 DEPOSITION.

21 Q ALL RIGHT. NOW, YOU'VE WRITTEN ON THE BOARD
22 "MEDIAN" AND "MEAN." ARE THOSE SOMETIMES REFERRED TO AS
23 "MEASURES OF CENTRAL TENDENCY"?

24 A YES, IN STATISTICAL LANGUAGE.

25 Q OKAY. AND IS -- WHEN YOU WRITE THE WORD
26 "MEAN," IS THAT THE SAME THING OR IS THAT DIFFERENT FROM
27 WHAT IS CALLED THE "ARITHMETIC MEAN"?

28 A IT WOULD BE THE SAME THING.

1 Q OKAY. AND WHAT IS THE ARITHMETIC MEAN?

2 A IT'S WHAT WE NORMALLY THINK OF AS THE
3 AVERAGE OF THE DISTRIBUTION OF OBSERVATIONS. YOU CAN
4 ESTIMATE IT SIMPLY BY TAKING THE SUM OF ALL THE
5 OBSERVATIONS -- IN THIS CASE, THE SUM OF ALL RATES OF
6 COFFEE CONSUMPTION -- AND DIVIDE IT BY THE NUMBER OF
7 RESPONDENTS, THE NUMBER OF PEOPLE IN THE SAMPLE.

8 Q OKAY. AND IN YOUR VIEW, IS THAT CONSISTENT
9 WITH THE REGULATION THAT SPEAKS OF --

10 CAN WE GO BACK TO THAT SLIDE.

11 -- THE AVERAGE RATE OF INTAKE?

12 A YES.

13 MR. SCHURZ: OBJECTION; CALLS FOR A LEGAL
14 CONCLUSION.

15 THE COURT: OVERRULED.

16 Q BY MR. METZGER: OKAY. SO THE REGULATION, I
17 SEE, USES THE TERM "AVERAGE" TWICE: ONCE FOR RATE OF
18 INTAKE AND ONCE FOR USERS. HOW DO YOU UNDERSTAND THAT?

19 MR. SCHURZ: SAME OBJECTION; CALLS FOR A LEGAL
20 CONCLUSION.

21 THE COURT: OVERRULED.

22 THE WITNESS: THE AVERAGE CONSUMER WOULD BE A
23 PERSON WHO, IN MY OPINION, REGULARLY CONSUMES COFFEE.
24 SO I WOULD SAY IT WOULD BE A PERSON WHOSE COFFEE
25 CONSUMPTION IS GREATER THAN OR EQUAL TO A CUP A DAY.

26 Q BY MR. METZGER: OKAY. AND --

27 THE COURT: LET ME ASK YOU THIS: IN PARAGRAPH 24
28 OF THE PETERSEN DECLARATION, DOES DR. PETERSEN STATE HER

1 EXPLANATION OF "AVERAGE" AS MEANING "TYPICAL," OR IS
2 THAT YOUR INTERPRETATION?

3 THE WITNESS: WHAT SHE STATES IN HER DECLARATION
4 IS THAT SHE IS INTERPRETING "AVERAGE," IN THIS CONTEXT,
5 TO MEAN "TYPICAL."

6 THE COURT: DID SHE EXPLAIN WHAT "TYPICAL" MEANS,
7 TO BE A MEDIAN, OR THAT'S YOUR INTERPRETATION?

8 THE WITNESS: NO. SHE ACTUALLY REFERS TO IT AS
9 THE "GEOMETRIC MEAN" --

10 THE COURT: OKAY.

11 THE WITNESS: -- WHICH IS ESSENTIALLY EQUIVALENT,
12 IN THIS CONTEXT, TO THE MEDIAN VALUE. THEY BOTH
13 REPRESENT THE 50TH PERCENTILE VALUE.

14 THE COURT: ALL RIGHT.

15 Q BY MR. METZGER: OKAY. NOW, YOU DREW ON THE
16 BOARD -- IS IT FAIR TO CALL THAT A SKEWED BELL CURVE, OR
17 HOW DO YOU DESCRIBE THAT?

18 A WELL, THE NORMAL DISTRIBUTION, IT'S USUALLY
19 REFERRED TO AS A BELL-SHAPED CURVE BECAUSE IT'S
20 SYMMETRICAL. IN A NORMAL DISTRIBUTION, THE MEAN AND THE
21 MEDIAN WOULD BE THE SAME. THE MEAN AND THE GEOMETRIC
22 MEAN WOULD BE THE SAME.

23 BUT WHEN YOU HAVE A SKEWED DISTRIBUTION, YOU
24 START TO SEE THE SEPARATION FROM THE MEDIAN VALUE AND
25 THE MEAN VALUE.

26 Q OKAY. AND WHEN YOU HAVE THIS SKEWED
27 DISTRIBUTION, DOES THAT NECESSARILY MANDATE THAT ONE USE
28 THE GEOMETRIC MEAN AS THE MEASURE OF CENTRAL TENDENCY?

1 A WHEN YOU HAVE A SKEWED DISTRIBUTION? NO,
2 NOT AT ALL.

3 THE GEOMETRIC MEAN, THE MEDIAN, THE MEAN
4 VALUE, CAN BE APPLIED TO ANY DISTRIBUTION DATA. IT
5 DOESN'T MATTER WHAT THE SHAPE IS.

6 THE MAGNITUDE OF THOSE MEASURES WILL BE
7 DIFFERENT, DEPENDING ON THE SHAPE, BUT THERE'S NO
8 PRECONCEIVED -- OR THERE'S NO -- THERE'S NO REASON THAT
9 ONE WOULD USE ONE MEASURE OR ANOTHER SIMPLY BECAUSE OF
10 THE UNDERLYING SHAPE OF THE DISTRIBUTION. THEY'RE ALL
11 EQUALLY USABLE.

12 Q OKAY. NOW, DR. PETERSEN TESTIFIED THAT,
13 BASED UPON HER USE OF HER ANALYSIS OF THE NHANES DATA
14 AND THE USE OF THE GEOMETRIC MEAN, SHE CALCULATED THE
15 CONSUMPTION OF COFFEE TO BE 0.69 CUPS PER DAY.

16 IS THAT WHAT YOU SAW?

17 A 0.68, I THINK.

18 Q 0.68; I'M SORRY. OKAY.

19 A YES, THAT'S CORRECT.

20 Q AND IN YOUR OPINION, DOES THAT LEVEL OF
21 CONSUMPTION OF COFFEE ACCURATELY STATE THE CONSUMPTION
22 OF COFFEE BY AN AVERAGE CONSUMER?

23 A NO, IT DOES NOT.

24 Q DOES IT UNDERESTIMATE IT, IN YOUR OPINION?

25 A YES, IT SIGNIFICANTLY UNDERESTIMATES.

26 Q HOW SIGNIFICANTLY?

27 A I WOULD ESTIMATE THE AVERAGE RATE OF COFFEE
28 CONSUMPTION, BASED UPON A SURVEY CONDUCTED BY THE

1 NATIONAL COFFEE ASSOCIATION, TO BE ROUGHLY THREE CUPS
2 PER DAY.

3 Q OKAY. NOW, ARE YOU REFERRING TO THE ANNUAL
4 SURVEY THAT THE NATIONAL COFFEE ASSOCIATION PUBLISHES?

5 A YES. THE 2013 SURVEY.

6 Q OKAY. AND DO YOU CONSIDER THAT SURVEY, THE
7 ANNUAL SURVEY PUBLISHED BY THE NATIONAL COFFEE
8 ASSOCIATION, TO BE THE TYPE OF PUBLICATION ON WHICH AN
9 EXPERT IN EXPOSURE ASSESSMENT WOULD REASONABLY RELY?

10 A YES.

11 MR. SCHURZ: OBJECTION. THERE'S NO FOUNDATION AS
12 TO WHETHER THIS WITNESS IS ENGAGED IN DIETARY EXPOSURE
13 ASSESSMENT AND WOULD HAVE ANY BASIS FOR UNDERSTANDING
14 THAT.

15 THE COURT: OVERRULED. YOU CAN CROSS-EXAMINE HIM.

16 THE WITNESS: WOULD YOU REPEAT THE QUESTION.

17 Q BY MR. METZGER: YES. DO YOU CONSIDER THAT
18 SURVEY TO BE THE TYPE OF PUBLICATION UPON WHICH AN
19 EXPERT IN THE FIELD OF EXPOSURE ASSESSMENT WOULD
20 REASONABLY RELY?

21 A YES, I DO.

22 Q WHY DO YOU CONSIDER IT TO BE REASONABLE FOR
23 AN EXPERT IN EXPOSURE ASSESSMENT TO RELY ON THE NCA'S
24 SURVEYS?

25 A WELL, THE NCA, I UNDERSTAND, HAS A LONG
26 HISTORY OF CONDUCTING SURVEYS. THEY'RE INTERESTED IN
27 TRENDS OF COFFEE CONSUMPTION TO PROVIDE TO PRIVATE
28 GROUPS WHO PRODUCE OR MAKE COFFEE, SELL COFFEE. THEY'VE

1 BEEN DOING THIS, I THINK, FOR MORE THAN 50 YEARS.

2 EACH YEAR THEY PRESENT A SURVEY. THE SAMPLE
3 THAT I USED, AND WHAT WAS VERY TYPICAL OF WHAT THEY DID
4 IN PRIOR YEARS, HAS ABOUT 2,000 ADULT RESPONDENTS IN THE
5 U.S.

6 THE RESPONDENTS ARE SELECTED IN A -- IN WHAT
7 SEEMS TO BE A RIGOROUS PROCESS OF RANDOMIZATION AND WITH
8 SOME APPRECIATION FOR ALSO INCLUDING MINORITY GROUPS
9 THAT THEY'RE INTERESTED IN GETTING DEMOGRAPHICS FOR.

10 AND IT'S FOCUSED ENTIRELY ON COFFEE. IT
11 INCLUDES A WIDE RANGE OF CONSUMPTION RATES, GOING UP TO
12 GREATER THAN TEN CUPS PER DAY.

13 AND OTHER INVESTIGATORS THAT HAVE BEEN
14 TRYING TO ESTIMATE EXPOSURES TO COFFEE FOR PURPOSES OF
15 ESTABLISHING RISKS TO HEALTH HAVE USED NCA SURVEY DATA.

16 Q SUCH AS?

17 A THE INTERNATIONAL AGENCY FOR RESEARCH ON
18 CANCER HAS USED IT, I THINK, IN THE CONTEXT OF
19 ACRYLAMIDE. THERE WAS ALSO A REPORT --

20 MR. SCHURZ: OBJECTION, YOUR HONOR. THIS DOCUMENT
21 WAS NEVER PRODUCED. THERE'S NO RELIANCE MATERIALS IN
22 DR. RAPPAPORT'S MATERIALS THAT SUGGEST ANYTHING LIKE
23 THIS.

24 THE COURT: OBJECTION OVERRULED.

25 THE WITNESS: THERE WAS ALSO A REPORT THAT WAS
26 COMMISSIONED BY THE FOOD AND DRUG ADMINISTRATION TO
27 ESTIMATE THE AMOUNTS OF CAFFEINE THAT WERE INGESTED BY
28 THE U.S. POPULATION AND SUSCEPTIBLE GROUPS --

1 MR. SCHURZ: AGAIN, YOUR HONOR, WE'D OBJECT. THIS
2 IS -- DR. RAPPAPORT IS OFFERING REFERENCE TO MATERIALS
3 THAT HE DID NOT PRODUCE, THAT HE NEVER INDICATED AS A
4 PART OF HIS OPINIONS, AND ARE COMING UP FOR THE FIRST
5 TIME.

6 THE COURT: OBJECTION OVERRULED.

7 THE WITNESS: AND THE EXPERT WHO WROTE THAT REPORT
8 ALSO RELIED HEAVILY ON THE NCA DATA.

9 Q BY MR. METZGER: OKAY. NOW I'D LIKE TO ASK
10 YOU ABOUT THE NHANES DATA. IS THAT THE DATA THAT DR.
11 PETERSEN RELIED ON?

12 A YES.

13 Q AND DO YOU HAVE ANY CRITICISMS OF DR.
14 PETERSEN'S RELIANCE ON THE NHANES DATA?

15 A YES, TO A CERTAIN EXTENT. THE NHANES DATA
16 WERE COLLECTED FOR PERIODS PRIMARILY THROUGH 2006. SOME
17 OF THE DATA CAME A BIT MORE RECENTLY, IN 2010. SO THEY
18 WERE OLDER, BY HISTORICAL STANDARDS, THAN CURRENT RATES
19 OF COFFEE CONSUMPTION.

20 NHANES IS ALSO A VERY LARGE SURVEY OF ALL
21 FOOD ITEMS, NOT SIMPLY COFFEE. SO IT WASN'T FOCUSED ON
22 COFFEE.

23 AND IT INCLUDED AS THE HIGHEST RATE OF
24 COFFEE CONSUMPTION SIX CUPS PER DAY. AND WE KNOW FROM
25 THE NCA ANALYSES THAT SOMETHING LIKE 8 TO 10 PERCENT OF
26 RESPONDENTS DRANK MORE THAN SIX CUPS PER DAY. AND THAT
27 WOULD HAVE BEEN UNDERESTIMATED, THEN, IN THE NHANES
28 DATA.

1 Q AND WHAT IS THE SIGNIFICANCE, THAT THE
2 NHANES DATA TRUNCATED -- IF WE CAN USE THAT WORD --
3 EXPOSURE AT SIX CUPS PER DAY?

4 A IT WOULD UNDERESTIMATE THE AVERAGE EXPOSURE,
5 AGAIN, BECAUSE IT'S THE LARGE -- PEOPLE THAT CONSUME THE
6 MOST COFFEE THAT CONTRIBUTE A BIT DISPROPORTIONATELY TO
7 THE AVERAGE.

8 Q AND WHAT IS THE SIGNIFICANCE TO YOU THAT DR.
9 PETERSEN INCLUDED WITHIN HER ANALYSIS CONSUMPTION OF
10 COFFEE BY CHILDREN?

11 A WELL, I THINK IT'S COMPLETELY INAPPROPRIATE
12 BECAUSE THERE'S NO WAY THAT SUCH POPULATIONS OF
13 NONCONSUMERS COULD BE REGARDED AS AVERAGE CONSUMERS.

14 Q AND WHAT IS THE EFFECT OF INCLUDING CHILDREN
15 IN A CONSUMPTION ANALYSIS?

16 A WELL, AS I SAID, I THINK IT'S INAPPROPRIATE
17 BECAUSE CHILDREN DON'T CONSUME.

18 Q AND WHAT IS THE EFFECT OF THAT, NUMERICALLY?

19 A IT REDUCES THE ESTIMATE OF THE AVERAGE RATE.

20 Q OKAY. NOW, AMONG THE MATERIALS THAT YOU
21 RECEIVE, DO YOU ACTUALLY RECEIVE THE -- I'LL CALL IT THE
22 RAW DATA, FROM THE NCA STUDY?

23 A I DIDN'T RECEIVE THE RAW DATA. I RECEIVED A
24 COMPILATION OF GROUPED DATA.

25 Q WHAT DO YOU MEAN BY THAT?

26 A SO IN THE NCA STUDY, THEY CATEGORIZE
27 PEOPLE'S COFFEE CONSUMPTION IN TERMS OF CUPS PER DAY.

28 SO IN THE DATA THAT I RECEIVED, I DIDN'T

1 HAVE EACH RESPONDENT'S RESPONSE AS TO HOW MANY CUPS PER
2 DAY HE OR SHE HAD CONSUMED, BUT I DID RECEIVE SUBJECTS
3 WHO HAD REPORTED -- THE TOTAL NUMBER OF SUBJECTS THAT
4 REPORTED ONE CUP A DAY, TWO CUPS A DAY, THREE, UP TO TEN
5 OR MORE.

6 SO THOSE ARE GROUP DATA. AND FROM THOSE, I
7 WAS ABLE TO MORE OR LESS RECONSTRUCT THIS DISTRIBUTION
8 SHOWN SCHEMATICALLY HERE ON MY DRAWING.

9 Q OKAY. AND HOW DID YOU DO THAT?

10 A I SIMPLY ENTERED THESE GROUPS' DATA AND THE
11 DIFFERENT NUMBER OF CUPS PER DAY INTO A STANDARD
12 STATISTICAL PACKAGE AND REPRODUCED THE DISTRIBUTION AND
13 ESTIMATED THE MEAN VALUE, ESTIMATED THE MEDIAN VALUE,
14 AND THE GEOMETRIC MEAN VALUE, AND SO ON.

15 MR. METZGER: OKAY.

16 THE COURT: WE'RE GOING TO HAVE TO RECESS AT THIS
17 TIME. WE'LL RESUME AT 1:30.

18 DR. RAPPAPORT, YOU'RE ORDERED TO RETURN AT
19 1:30.

20 THANK YOU, COUNSEL.

21 (AT 11:49 A.M., A LUNCH RECESS WAS TAKEN
22 UNTIL 1:30 P.M. OF THE SAME DAY.)

23 (TRANSCRIPT CONTINUES ON PAGE 151.)

24

25

26

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EXHIBIT “E”

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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT 323

HON. ELIHU M. BERLE, JUDGE

COUNCIL FOR EDUCATION AND RESEARCH ON)
TOXICS, A CALIFORNIA CORPORATION,)

PLAINTIFF,)

VS.)

CASE NO.
BC435759

STARBUCKS CORPORATION, A CALIFORNIA)
CORPORATION, ET AL.,)

DEFENDANTS.)

AND CONSOLIDATED ACTION.)

REPORTER'S TRANSCRIPT OF TRIAL PROCEEDINGS

TUESDAY, SEPTEMBER 30, 2014

AFTERNOON SESSION

APPEARANCES:

FOR THE PLAINTIFF: METZGER LAW GROUP
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CCROLA JOB
NO. 114597

KAREN VILICICH, CSR. NO. 7634
OFFICIAL REPORTER PRO TEMPORE

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I N D E X

TUESDAY, SEPTEMBER 30, 2014 (P.M.)

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1 CASE NUMBER: BC435759
2 CASE NAME: CERT VS. STARBUCKS
3 LOS ANGELES, CALIFORNIA TUESDAY, SEPTEMBER 30, 2014
4 DEPARTMENT 323 HON. ELIHU M. BERLE, JUDGE
5 REPORTER: KAREN VILICICH, CSR NO. 7634
6 TIME: P.M. SESSION
7

8 (THE FOLLOWING PROCEEDINGS WERE HELD
9 IN OPEN COURT:)

10
11 THE COURT: BACK ON THE RECORD IN THE CASE OF CERT
12 VERSUS STARBUCKS. ALL COUNSEL ARE PRESENT AND
13 PROFESSOR RAPPAPORT IS ON THE STAND.

14 THE CLERK: SIR, YOU HAVE PREVIOUSLY BEEN SWORN AND
15 YOU ARE STILL UNDER OATH.

16 PLEASE RESTATE YOUR NAME FOR THE RECORD.

17 THE WITNESS: STEVEN RAPPAPORT.

18 THE COURT: GOOD AFTERNOON, PROFESSOR RAPPAPORT.
19 MR. METZGER WAS INQUIRING. COUNSEL WILL PROCEED.

20
21 DIRECT EXAMINATION (CONTINUED)

22
23 BY MR. METZGER:

24 Q YES, DR. RAPPAPORT, WOULD YOU INFORM THE
25 COURT HOW YOUR CONCLUSION REGARDING THE CONSUMPTION OF
26 COFFEE IN THE UNITED STATES POPULATION COMPARES TO THAT
27 OF DR. PETERSEN?

28 A YES. DR. PETERSEN ESTIMATED THAT THE COFFEE

1 CONSUMPTION WAS .68 CUPS PER DAY, AND THAT WAS ESTIMATED
2 AS THE GEOMETRIC MEAN FROM DATA THAT SHE HAD GATHERED
3 FROM NHANES. I ESTIMATED THAT THE COFFEE CONSUMPTION WAS
4 3.03, I THINK, CUPS PER DAY. THIS WAS BASED UPON MY
5 CALCULATIONS INVOLVING THE GROUP DATA THAT I HAD RECEIVED
6 FROM THE NATIONAL COFFEE ASSOCIATION. SO MY ESTIMATE WAS
7 ROUGHLY FOUR TIMES HER ESTIMATE.

8 Q OKAY, AND HOW DOES THE NATIONAL COFFEE
9 ASSOCIATION'S ESTIMATE OF COFFEE CONSUMPTION BASED UPON A
10 GEOMETRIC MEAN COMPARE WITH THAT OF DR. PETERSEN?

11 A I ESTIMATED THE GEOMETRIC MEAN FROM MY
12 ANALYSIS OF THE N.C.A. DATA TO BE 2.4 CUPS PER DAY.

13 Q HERS WAS ZERO POINT --

14 A 0.68, SO ROUGHLY THREE TIMES.

15 MR. METZGER: THANK YOU, DR. RAPPAPORT. I HAVE NO
16 FURTHER QUESTIONS.

17

18 CROSS-EXAMINATION

19

20 BY MR. SCHURZ:

21 Q GOOD AFTERNOON, DR. RAPPAPORT.

22 A GOOD AFTERNOON.

23 Q SO IN THIS CASE, YOU DID NOT REVIEW THE
24 UNDERLYING EXPOSURE ASSESSMENT, WHAT HAS BEEN MARKED AS
25 DEFENDANT'S EXHIBIT 10742, PREPARED BY DR. PETERSEN, IN
26 FORMING YOUR OPINIONS; CORRECT?

27 A NO, I BASED IT UPON HER DEPOSITION AND THE
28 EXHIBITS ATTACHED TO IT.

1 Q YOU DID NOT PERFORM AN EVALUATION OF
2 DR. PETERSEN'S EXPOSURE ASSESSMENT AS PART OF YOUR WORK
3 IN THIS CASE; CORRECT?

4 A THAT IS CORRECT IN THE SENSE THAT I DID NOT
5 READ HER OFFICIAL EXPOSURE ASSESSMENT.

6 Q AND YOUR OPINIONS WITH RESPECT TO
7 DR. PETERSEN'S EXPOSURE ASSESSMENT ARE LIMITED TO THE
8 VALUE THAT SHE CALCULATED RELATING TO THE FREQUENCY OF
9 COFFEE CONSUMPTION; IS THAT CORRECT?

10 A NOT ENTIRELY. SHE PRESENTED A NUMBER OF
11 TABLES IN HER EXHIBITS THAT I REVIEWED, AND THESE WERE
12 PART OF MY EVALUATION.

13 Q MY QUESTION IS: DR. RAPPAPORT, YOUR
14 OPINIONS WITH RESPECT TO DR. PETERSEN'S EXPOSURE
15 ASSESSMENT ARE LIMITED TO THE FREQUENCY OF CONSUMPTION OF
16 COFFEE; IS THAT CORRECT?

17 MR. METZGER: OBJECTION; ASKED AND ANSWERED.

18 THE COURT: OVERRULED.

19 THE WITNESS: NO. DR. PETERSEN DID SEVERAL
20 ANALYSES. THE ONES THAT I INVESTIGATED WERE RELATED TO
21 THE AMOUNT OF COFFEE THAT WAS CONSUMED I THINK PER EATING
22 OCCASION AND THE OTHER WAS THE RATE OF CONSUMPTION ACROSS
23 THE U.S. POPULATION. SO THOSE ARE TWO DIFFERENT
24 CALCULATIONS THAT SHE HAD PERFORMED USING THE NHANES
25 DATA. I REVIEWED BOTH OF THOSE.

26 Q BY MR. SCHURZ: WHAT CONCLUSIONS DID YOU
27 REACH WITH RESPECT TO THE AMOUNT OF COFFEE CONSUMED PER
28 EATING OCCASION?

1 A I WOULD HAVE TO LOOK AT THE TABLE TO GIVE
2 YOU THE QUANTITATIVE ANSWER TO THAT.

3 Q PERHAPS WE WILL GET TO THAT LATER.
4 DR. RAPPAPORT, YOU DO NOT CONSIDER YOURSELF
5 AN EXPERT ON DIETARY EXPOSURE ANALYSIS; CORRECT?

6 A THAT IS CORRECT.

7 Q YOU DO NOT CONSIDER YOURSELF AN EXPERT ON
8 THE SURVEY DESIGN OF FOOD FREQUENCY QUESTIONNAIRES;
9 CORRECT?

10 A CORRECT.

11 Q YOU DO NOT CONSIDER YOURSELF AN EXPERT IN
12 THE AREA OF RISK ASSESSMENT; CORRECT?

13 A THAT'S CORRECT.

14 Q AND YOU HAVE NEVER CONDUCTED A
15 PROPOSITION 65 RISK ASSESSMENT?

16 A THAT'S CORRECT.

17 Q YOU HAVE NEVER CONDUCTED A QUANTITATIVE RISK
18 ASSESSMENT UNDER PROPOSITION 65?

19 A THAT'S CORRECT.

20 Q AND YOU ARE NOT FAMILIAR WITH THE
21 REGULATIONS FOR PREPARING A RISK ASSESSMENT UNDER
22 PROPOSITION 65; CORRECT?

23 A THAT'S CORRECT.

24 Q NOW, YOU HAVE NEVER MADE A PRESENTATION TO
25 OEHHWA RELATING TO THE LISTING OF A PROPOSITION 65
26 CHEMICAL; CORRECT?

27 A NO, I HAVE NOT.

28 Q YOU HAVE NEVER LECTURED OR TAUGHT ABOUT

1 PROPOSITION 65 AS PART OF YOUR TEACHING RESPONSIBILITIES
2 AND COURSE WORK; CORRECT?

3 A NO, I HAVE NOT.

4 Q YOU HAVE NEVER WRITTEN ABOUT PROPOSITION 65
5 IN ANY JOURNAL OR PEER-REVIEWED ARTICLE; CORRECT?

6 THE COURT: LET ME SHORT-CIRCUIT THIS. I AM SURE
7 THERE ARE THINGS THAT DR. PETERSEN (SIC) NEVER DID. WHY
8 DON'T WE JUST FOCUS ON WHAT HE TESTIFIED THAT HE DID DO?

9 MR. SCHURZ: THANK YOU, YOUR HONOR.

10 Q NOW, YOU HAVE OFFERED AN OPINION WITH
11 RESPECT TO SECTION 25721 OF THE CALIFORNIA CODE OF
12 REGULATIONS; CORRECT?

13 A YES.

14 Q THAT OPINION IS BASED UPON YOUR REVIEW OF
15 THE REGULATION; CORRECT?

16 A YES, REVIEW OF THE WORDING OF THE
17 REGULATION.

18 Q YOU READ THE REGULATION, SECTION 25721, FOR
19 THE FIRST TIME THE DAY BEFORE YOUR DEPOSITION; CORRECT?

20 A THAT'S CORRECT.

21 Q NOW, PRIOR TO THAT TIME -- AND YOUR
22 DEPOSITION WAS APRIL THE 21ST OF 2014; CORRECT?

23 A YES, I THINK SO.

24 Q SO YOU READ IT FOR THE FIRST TIME ON APRIL
25 THE 20TH OF 2014; CORRECT?

26 A YES.

27 Q PRIOR TO THAT TIME, PRIOR TO APRIL THE 20TH,
28 YOU HAD NEITHER IDENTIFIED NOR LOCATED SECTION 25271;

1 CORRECT?

2 A THAT'S CORRECT.

3 Q NOW -- AND YOU REVIEWED THAT IN A MEETING
4 WITH MR. METZGER; CORRECT?

5 A YES.

6 Q SO THE DAY BEFORE YOUR DEPOSITION, YOU ARE
7 PREPARING TO BE DEPOSED THE NEXT DAY; CORRECT?

8 A YES.

9 Q AND AS PART OF THAT PREPARATION, YOU LOOKED
10 FOR THE FIRST TIME AT REGULATION 25721; CORRECT?

11 A YES.

12 Q AND BASED UPON YOUR REVIEW WITH MR. METZGER
13 THE DAY BEFORE YOUR DEPOSITION, YOU FORMED AN OPINION
14 WITH RESPECT TO THE USE OF THE TERM "AVERAGE" WITHIN
15 SECTION 25721; CORRECT?

16 A YES.

17 Q NOW, IN THAT REVIEW, YOU FORMED AN OPINION
18 SPECIFICALLY THAT AN AVERAGE COFFEE CONSUMER IS A PERSON
19 WHO CONSUMES AT LEAST ONE CUP OF COFFEE PER DAY; CORRECT?

20 A YES, THAT WAS MY OPINION.

21 Q SO YOUR DEFINITION OF AVERAGE COFFEE
22 CONSUMER EXCLUDES ALL PERSONS WHO WOULD CONSUME LESS THAN
23 ONE CUP OF COFFEE PER DAY; CORRECT?

24 A YES.

25 Q NOW, DO YOU HAVE AN UNDERSTANDING OF WHAT
26 PERCENTAGE OF COFFEE DRINKERS CONSUME LESS THAN ONE CUP
27 OF COFFEE PER DAY?

28 A YES.

1 Q HOW -- WHAT PERCENTAGE OF COFFEE CONSUMERS
2 DRINK LESS THAN ONE CUP OF COFFEE PER DAY?

3 A WELL, FROM THE N.C.A. SURVEY, THEY PRESENTED
4 THE STATISTIC SHOWING THE NUMBER OF AMERICANS WHO
5 RESPONDED THAT THEY HAD HAD AT LEAST ONE CUP OF COFFEE ON
6 THE DAY PRECEDING THE SURVEY, AND IN 2013, THAT WOULD
7 HAVE BEEN 47 PERCENT. I'M SORRY, 37 PERCENT.

8 Q IS IT YOUR TESTIMONY, DR. RAPPAPORT, THAT 37
9 PERCENT OF COFFEE CONSUMERS DRINK LESS THAN ONE CUP OF
10 COFFEE PER DAY?

11 A NO, 37 PERCENT OF AMERICANS DRINK LESS THAN
12 ONE CUP OF COFFEE PER DAY ACCORDING TO THE SURVEY. IT
13 DOES NOT MEAN THAT THEY ARE CONSUMERS.

14 Q NOW, YOU DO NOT INCLUDE AS PART OF YOUR
15 CALCULATIONS THAT 37 PERCENT OF THE POPULATION WHO
16 CONSUME LESS THAN ONE CUP OF COFFEE PER DAY; CORRECT?

17 A NO, BECAUSE I WOULD NOT REGARD THEM AS
18 AVERAGE CONSUMERS.

19 Q THAT, AGAIN, IS BASED UPON YOUR READING OF
20 SECTION 25721, WHICH YOU DID THE DAY BEFORE YOUR
21 DEPOSITION; CORRECT?

22 A YES.

23 Q NOW, SO UNDER YOUR DEFINITION OF "AVERAGE,"
24 DR. RAPPAPORT, SOMEONE WHO DRINKS COFFEE FOUR TIMES A
25 WEEK FOR 40 YEARS WOULD NOT BE COUNTED IN YOUR
26 CALCULATION OF AN AVERAGE RATE OF INTAKE FOR THE AVERAGE
27 CONSUMER; CORRECT?

28 A THAT IS CORRECT.

1 Q NOW, YOU MENTIONED NHANES AS INCLUDING
2 CONSUMERS OF COFFEE WHO CONSUME LESS THAN ONE CUP OF
3 COFFEE PER DAY; CORRECT?

4 A YES.

5 Q AND IS IT YOUR UNDERSTANDING THAT THE DATA
6 RELIED UPON BY DR. PETERSEN AS PART OF THAT NHANES DATA
7 SET INCLUDED PEOPLE WHO DON'T DRINK COFFEE AT ALL?

8 A YES, HAD TO HAVE BEEN.

9 Q YOUR UNDERSTANDING IS THAT DR. PETERSEN'S
10 ANALYSIS INCLUDED NON-CONSUMERS OF COFFEE?

11 A YES. I DON'T SEE HOW SHE COULD HAVE COME UP
12 WITH WHAT SHE DID.

13 Q HAVE YOU REVIEWED THE NHANES DATA THAT WAS
14 THE BASIS FOR DR. PETERSEN'S CONCLUSION?

15 A I REVIEWED DR. PETERSEN'S TABLES THAT HAD
16 BEEN SUMMARIZED FROM THE NHANES DATA. ON THE BASIS OF
17 THAT, I WOULD SAY THAT .68 CUPS OF COFFEE PER DAY WAS NOT
18 REALISTIC.

19 Q NOW, SHOWING YOU WHAT HAS BEEN IDENTIFIED AS
20 DEFENDANTS' EXHIBIT 10742.

21 DO YOU HAVE EXHIBIT 10742 IN FRONT OF YOU,
22 DR. RAPPAPORT?

23 A YES, I ASSUME THAT IS WHAT IS SHOWN ON THE
24 COMPUTER SCREEN HERE.

25 Q YES, IT IS.

26 A ALL RIGHT.

27 Q IF YOU WOULD WANT TO SEE THE HARD COPY, IT
28 IS THE SECOND TO LAST TAB IN EXHIBIT 10742.

1 DO YOU HAVE IT IN FRONT OF YOU?

2 A YES, I DO.

3 Q NOW, DIRECTING YOUR ATTENTION,
4 DR. RAPPAPORT, TO THE FAR LEFT-HAND COLUMN, WHERE IT
5 INDICATES THE AMOUNT OF COFFEE CONSUMED, DO YOU SEE THAT
6 COLUMN THERE ON THE FAR LEFT-HAND SIDE?

7 A I DO.

8 Q NOW, AND THE "VALUES" SHOW VALUES THAT WOULD
9 BE LESS THAN ONCE A MONTH AT 0.2, AND THEN INCREASING
10 VALUES OF TWO TO THREE TIMES A MONTH, ONCE A MONTH, ET
11 CETERA, UNTIL WE GET ALL THE WAY TO ONE CUP A DAY, 2.5
12 CUPS A DAY, 4.5 CUPS A DAY AND SEVEN.

13 DO YOU SEE THAT?

14 A I DO.

15 Q NOW, YOU UNDERSTAND THAT THIS IS THE SET OF
16 VALUES OR DATA THAT DR. PETERSEN RELIED UPON IN
17 CALCULATING HER AVERAGE RATE OF FREQUENCY; CORRECT?

18 A I ASSUME SO.

19 Q AND ON ALL OF THE RESPONDENTS, THE -- ALL OF
20 THEM WHO ARE IDENTIFIED, IF WE COULD JUST ENLARGE THIS A
21 LITTLE BIT TO CAPTURE THE RIGHT-HAND COLUMN, ALL OF THE
22 PEOPLE WHO ARE IDENTIFIED, THE 5,781 ARE IDENTIFIED AS
23 USERS; CORRECT?

24 A I DON'T SEE WHERE THE 5,781 COMES FROM.

25 Q TAKE A LOOK AT THE HARD COPY. MAYBE WE
26 COULD -- CAN WE ENLARGE THIS?

27 LET'S START OVER AND LET'S CAPTURE THE
28 RIGHT-HAND SIDE, PLEASE.

1 LOOKING OVER AT THE FAR RIGHT-HAND SIDE.

2 NO, SORRY, TOM.

3 DO YOU SEE THAT THE NUMBER OF USERS IS
4 IDENTIFIED AS 5,781?

5 A YES.

6 Q AND YOU UNDERSTAND THAT THE NHANES DATA THAT
7 BARBARA PETERSEN WAS RELYING UPON IS USED EXCLUSIVELY FOR
8 COFFEE CONSUMERS OR COFFEE USERS AS DEFINED IN THIS
9 TABLE; CORRECT?

10 A COFFEE USERS I THINK WOULD BE A BETTER TERM,
11 YES.

12 Q SO IT DOES NOT, IN FACT, INCLUDE PEOPLE WHO
13 DON'T DRINK COFFEE AT ALL; CORRECT?

14 A WELL, IT DEPENDS ON WHAT YOU MEAN BY "AT
15 ALL." IF A PERSON DRINKS ONE CUP OF COFFEE EVERY THREE
16 MONTHS, I WOULD NOT REGARD THAT PERSON AS A CONSUMER OF
17 COFFEE. MAYBE A USER, A VERY OCCASIONAL USER, BUT NOT A
18 CONSUMER.

19 Q OKAY. LET'S TAKE A LOOK, IF WE CAN, AT THE
20 CUMULATIVE VALUES NOW WITH RESPECT TO THE NUMBER OF
21 RESPONDENTS, NUMBER OF USERS WHO INDICATE DRINKING
22 SOMETHING LESS THAN ONE CUP OF COFFEE PER DAY.

23 IF I COULD DIRECT YOUR ATTENTION,
24 DR. RAPPAPORT, TO THE COLUMN THAT IS THE SECOND FROM THE
25 RIGHT.

26 DO YOU SEE WHERE IT SAYS "CUMULATIVE"?

27 A YES.

28 Q AND DO YOU UNDERSTAND THAT WHAT IS BEING

1 REFLECTED HERE IS THE NUMBER OF COFFEE USERS AS DEFINED
2 BY NHANES AND THEIR CUMULATIVE TOTALS AS IT RELATES TO
3 EACH OF THE CONSUMPTION CATEGORIES THAT NHANES MEASURED?

4 A YES.

5 Q AND DIRECTING YOUR ATTENTION DOWN TO THE
6 COLUMN THAT HAS "0.79."

7 DO YOU SEE THAT THERE?

8 A YES, I DO.

9 Q THAT INDICATES THAT 39 PERCENT CUMULATIVE,
10 39 PERCENT OF THE USERS CAPTURED WITHIN THE NHANES FOOD
11 FREQUENCY QUESTIONNAIRE INDICATED THAT THEY DRINK COFFEE
12 LESS THAN ONE CUP PER DAY; CORRECT?

13 A YES, THAT IS REALLY QUITE SIMILAR TO WHAT
14 THE N.C.A. ESTIMATE IS.

15 Q YOU EXCLUDED ALL OF THESE PEOPLE FROM YOUR
16 DEFINITION OF "AVERAGE"; CORRECT?

17 A AN AVERAGE USER, YES. AN AVERAGE CONSUMER,
18 I AM SORRY.

19 Q NOW, THE -- YOU ALSO CRITICIZED -- YOU ALSO
20 CRITICIZED THE NHANES DATA SET FOR NOT QUANTIFYING THE
21 CONSUMPTION OF USERS WHO DRANK TEN OR MORE CUPS OF COFFEE
22 PER DAY; CORRECT?

23 A YES.

24 Q THAT WHAT NHANES DOES IS TO SAY THAT IF IT
25 IS IN EXCESS OF SIX CUPS PER DAY, THAT YOU WILL BE
26 TREATED AS DRINKING SEVEN CUPS PER DAY; CORRECT?

27 A WELL, DR. PETERSEN ASSUMED THEY CONSUMED SIX
28 CUPS PER DAY, BUT IF YOU TELL ME NHANES SAYS SEVEN CUPS A

1 DAY, I AM WILLING TO ACCEPT THAT.

2 Q WELL, WE WERE JUST LOOKING AT THE VALUES,
3 AND IS IT THE CASE THAT NHANES QUALIFIES ALL PEOPLE WHO
4 DRINK MORE THAN SIX CUPS PER DAY AS DRINKING SEVEN CUPS
5 PER DAY?

6 A I DON'T KNOW.

7 Q SO -- BUT YOU BELIEVE THAT THE NHANES DATA
8 SET UNDERESTIMATES CONSUMPTION OF COFFEE BECAUSE IT DOES
9 NOT CAPTURE THOSE HEAVY DRINKERS WHO DRINK UP TO TEN CUPS
10 PER DAY?

11 A TEN OR MORE.

12 Q SO IT UNDERESTIMATES SOME PORTION OF THE
13 POPULATION; CORRECT?

14 A YES.

15 Q IN YOUR OPINION.

16 NOW, THE PERCENTAGE THAT YOU EQUATE AS HEAVY
17 COFFEE DRINKERS IS ROUGHLY SIX PERCENT; CORRECT?

18 A BETWEEN SIX AND TEN. TEN OR MORE CUPS A
19 DAY, I THINK IT WAS EIGHT PERCENT FROM THE 2013 --

20 Q YOUR CONCERN IS THAT THE NHANES
21 UNDERESTIMATES THE VALUE WITH RESPECT TO THAT SIX TO TEN
22 PERCENT; CORRECT?

23 A I THINK THAT THAT SIX TO TEN PERCENT DOES
24 INCREASE THE AVERAGE RATE OF COFFEE CONSUMPTION, YES.

25 Q AND YOU WANT THOSE SIX TO EIGHT PERCENT TO
26 BE PROPERLY VALUED; CORRECT?

27 A YES.

28 Q BUT AT THE SAME TOKEN, THE 39 PERCENT CAN BE

1 EXCLUDED FROM YOUR AVERAGE CALCULATION; CORRECT?

2 A YES, BECAUSE IN MY OPINION, THEY WOULD NOT
3 REPRESENT AVERAGE USERS.

4 Q ALL RIGHT. NOW, THE EFFECT OF YOUR
5 ANALYSIS, DR. RAPPAPORT, BY SLICING OFF THAT 39 PERCENT
6 OR 37 PERCENT WHO DRINK LESS THAN ONE CUP OF COFFEE PER
7 DAY IS TO DRIVE THE ARITHMETIC MEAN HIGHER; IS IT NOT?

8 A NO. THE REGULATION SAYS THE AVERAGE
9 EXPOSURE OF THE AVERAGE USER. SO WE HAVE TO DECIDE WHAT
10 AN AVERAGE USER WOULD BE. IT COULD NOT BE SOMEONE WHO
11 DRINKS LESS THAN ONE CUP OF COFFEE A DAY. EVEN YOU HAVE
12 SHOWN THAT THE CUMULATIVE PERCENTAGE OF PERSONS IN THAT
13 CATEGORY WOULD BE, BASED UPON THE NHANES DATA, SOMETHING
14 LIKE 39 PERCENT, THAT CANNOT BE AN AVERAGE USER.

15 Q THAT IS BASED UPON YOUR READING OF THE
16 REGULATION FOR THE FIRST TIME THE DAY BEFORE YOUR
17 DEPOSITION; CORRECT?

18 A YES, THAT IS WHEN I READ IT THE FIRST TIME.

19 Q ALL RIGHT. LET'S TALK A LITTLE BIT ABOUT
20 YOUR BACKGROUND IN THE AREA OF THE NATIONAL HEALTH AND
21 NUTRITION EXAMINATION SURVEY.

22 YOU ARE FAMILIAR WITH THAT DATABASE;
23 CORRECT?

24 A YES.

25 Q AND YOU UNDERSTAND THAT THE NHANES DATABASE
26 IS SPECIFICALLY REFERENCED IN SECTION 25721(D)(4) OF THE
27 CALIFORNIA CODE OF RELATIONS; CORRECT?

28 A YES.

1 Q AS A DATA SET THAT IS SUITABLE FOR
2 PERFORMING AN EXPOSURE ANALYSIS IN PROPOSITION 65?

3 A YES.

4 Q NOW, YOU HAVE PERFORMED WHAT YOU DESCRIBED
5 AS A SUPERFICIAL REVIEW OF THE METHODOLOGY OF THE NHANES
6 PROGRAM; CORRECT?

7 A YES.

8 Q YOU HAVE NEVER TESTIFIED, OBVIOUSLY, ABOUT
9 NHANES BEFORE; CORRECT?

10 A I HAVE NOT.

11 Q AND YOU HAVE -- YOU HAVE NEVER HAD OCCASION
12 TO TEACH NHANES AS PART OF YOUR TEACHING EXPERIENCE;
13 CORRECT?

14 A I HAVE REFERRED TO NHANES, PARTICULAR SETS
15 OF NHANES DATA IN MY TEACHING.

16 Q BUT SPECIFICALLY, HAVE YOU HAD THE
17 OPPORTUNITY TO USE NHANES DATA IN ANY OF YOUR COURSES?

18 A IN MY COURSES?

19 I HAVE REFERRED TO SPECIFIC DATA SETS FROM
20 NHANES IN MY COURSES, YES.

21 Q NOW, YOU CONCLUDED IN THIS CASE THAT THE
22 N.C.A. DATA WAS PREFERABLE TO NHANES; CORRECT?

23 A YES, FOR REASONS I OUTLINED THIS MORNING.

24 Q AND IN MAKING THAT CONCLUSION, YOU DID NOT
25 CONDUCT ANY ANALYSIS TO DETERMINE THE BEST DATABASE FOR
26 CONSUMPTION DATA FOR CALCULATING THE AVERAGE RATE OF
27 INTAKE OF COFFEE FOR THE AVERAGE COFFEE DRINKER; CORRECT?

28 A WOULD YOU REPEAT THAT, PLEASE, SIR.

1 Q OF COURSE. YOU DID NOT CONDUCT ANY ANALYSIS
2 TO DETERMINE THE BEST DATABASE FOR CONSUMPTION DATA FOR
3 CALCULATING THE AVERAGE RATE OF INTAKE OF COFFEE FOR THE
4 AVERAGE COFFEE DRINKER; CORRECT?

5 A NO, I RELIED ON THE N.C.A. DATA BECAUSE I
6 REGARDED IT AS USEFUL FOR THAT PURPOSE.

7 Q ALL RIGHT. NOW, ONE OF THE CRITIQUES YOU
8 OFFERED WITH RESPECT TO NHANES IS THAT IT IS OUTDATED;
9 CORRECT?

10 A WELL, I THINK I DID USE THE TERM "OUTDATED"
11 IN THE SENSE THAT THE ESTIMATES THAT DR. PETERSEN RELIED
12 ON FROM NHANES WERE PRIMARILY FROM BEFORE 2006 OR
13 INCLUDING 2006.

14 Q AND IT IS YOUR OPINION THAT THE N.C.A. DATA
15 IS PREFERABLE BECAUSE IT REFLECTS AN INCREASE IN COFFEE
16 CONSUMPTION OVER THE LAST DECADE; CORRECT?

17 A YES, IT COULD REFLECT AN INCREASE IN COFFEE
18 CONSUMPTION.

19 Q NOT WHETHER IT COULD, IT IS YOUR BELIEF,
20 DR. RAPPAPORT, THAT, IN FACT, THE N.C.A. DATA HAS SHOWN
21 THAT THERE HAS BEEN AN INCREASE IN COFFEE CONSUMPTION
22 OVER THE LAST DECADE; CORRECT?

23 A WELL, I REVIEWED THE N.C.A. SUMMARY OF DATA
24 FROM 2009, AND AT THAT TIME, THE ESTIMATE OF PERSONS WHO
25 DID NOT CONSUME AT LEAST ONE CUP OF COFFEE PER DAY OR DID
26 NOT RESPOND TO HAVING DRANK A CUP OF COFFEE ON THE DAY
27 PRECEDING THE SURVEY WAS 54 PERCENT. IN 2013, IT WAS 63
28 PERCENT. SO, IN FACT, THERE HAD BEEN A NINE PERCENT

1 INCREASE BETWEEN 2009 AND 2013.

2 Q NOW, LET'S TAKE A LOOK AT THE N.C.A. STUDY
3 FROM 2013, THE DRINKING TRENDS SURVEY. IS THAT THE
4 DOCUMENT THAT YOU REVIEWED AS PART OF YOUR PREPARATION IN
5 THIS CASE?

6 A YES, THE DRINKING TRENDS SURVEY.

7 Q ALL RIGHT. SO IF WE COULD HAVE WHAT HAS
8 BEEN IDENTIFIED AND MARKED AS DX-10008.

9 DO YOU HAVE DX 10008 IN FRONT OF YOU?

10 A YES.

11 Q SO LET ME DIRECT YOUR ATTENTION,
12 DR. RAPPAPORT, TO THE SECOND TO LAST PAGE OF DX-10008.
13 IT IS MARKED WITH THE NUMBER AT THE BOTTOM IN THE
14 RIGHT-HAND CORNER, 0084.

15 DO YOU SEE THAT?

16 A YES.

17 Q NOW, LET'S TAKE A LOOK AT THE VALUE FOR
18 TOTAL COFFEE AS REPORTED BY N.C.A.

19 A YES.

20 Q YOU SEE FOR 2013, THE VALUE IS IDENTIFIED AS
21 3.20 CUPS PER DAY; CORRECT?

22 A YES.

23 Q AND AT -- IN 2009, IT SHOWS A CUPS PER DAY
24 OF 3.25; CORRECT?

25 A YES.

26 Q SO IN TERMS OF THE CUPS OF COFFEE CONSUMED
27 PER DAY, THERE IS -- ESSENTIALLY IT IS CONSTANT, IS IT
28 NOT, FROM 2009 TO 2013?

1 A YES, IN TERMS OF THE AVERAGE CONSUMPTION OF
2 SAY THE AVERAGE USER, THAT NUMBER HAS BEEN STABLE OVER
3 THE LAST TEN YEARS. HOWEVER, THE NUMBER OF PERSONS
4 CONSUMING COFFEE HAS, BY N.C.A. STATISTICS, HAS INCREASED
5 NINE PERCENT DURING THAT SAME PERIOD OF TIME.

6 Q BUT IN TERMS OF EVALUATING THE FREQUENCY
7 WITH WHICH COFFEE CONSUMERS CONSUME COFFEE, THE
8 CONSUMPTION LEVELS OVER THE LAST TEN YEARS HAVE REMAINED
9 CONSTANT; WOULD YOU AGREE?

10 A BY THE N.C.A. DATA, THE AVERAGE RATE OF
11 CONSUMPTION HAS REMAINED CONSTANT DURING THAT PERIOD,
12 YES.

13 Q IF ANYTHING, IT HAS GONE DOWN SLIGHTLY IN
14 THE LAST TWO YEARS, IN 2012 AND 2013, THAN WHAT WAS
15 REPORTED OVER THE COURSE OF THE LAST EIGHT TO TEN YEARS;
16 CORRECT?

17 A WELL, THE POINT ESTIMATES VARY FROM 3.16 TO
18 3.38, SO THERE IS SOME VARIABILITY THERE, YES.

19 Q BUT IN TERMS OF THE USE OF DATA FROM THE
20 NHANES PERIOD, WHICH, AS YOU HAVE INDICATED, WAS FROM
21 2003 TO 2006, AND IT INCLUDED UP TO 2010, THOSE VALUES,
22 AS REPORTED BY N.C.A., ARE NO DIFFERENT THAN WHAT IS
23 REPORTED FOR 2013; CORRECT?

24 A NO. I THINK I HAVE ANSWERED THAT QUESTION
25 TWICE NOW.

26 Q ALL RIGHT. NOW --

27 THE COURT: EXCUSE ME, CAN SOMEBODY TELL ME WHAT
28 SOLUBLE COFFEE IS?

1 MR. SCHURZ: I READ IT AS INSTANT.

2 THE COURT: THAT IS WHAT I THOUGHT. THEN AT THE
3 BOTTOM I SEE "INSTANT." ANYWAY, WE COULD FIGURE THAT OUT
4 LATER.

5 MR. SCHURZ: I CAN GIVE YOU SOME FURTHER GUIDANCE
6 ON IT, YOUR HONOR. THE METHODOLOGY WITH RESPECT TO THE
7 N.C.A. IN INCLUDING THE CATEGORIZATION AND IDENTIFICATION
8 OF COFFEE PRODUCTS CHANGED, AND SO WHAT YOU SEE AS
9 "SOLUBLE COFFEE" THEN WAS REDESIGNATED IN 2010 FORWARD AS
10 "INSTANT COFFEE."

11 MR. METZGER: COULD I CROSS-EXAMINE HIM ON THAT?

12 THE COURT: UNLESS IT IS A COFFEE ISSUE, WE WILL
13 JUST MOVE ON. I AM JUST CURIOUS.

14 Q BY MR. SCHURZ: SO LET'S TALK FURTHER WITH
15 RESPECT TO THE NHANES QUESTIONNAIRES AND THE DATA SET
16 THAT NHANES USED.

17 YOU HAVE INDICATED THAT YOU DON'T CONSIDER
18 YOURSELF AN EXPERT IN FOOD CONSUMPTION SURVEYS; CORRECT?

19 A YES, I HAVE SAID THAT.

20 Q AND YOU HAVE NOT HAD THE OPPORTUNITY TO
21 ACTUALLY REVIEW THE NHANES QUESTIONNAIRE THAT WAS PART OF
22 BARBARA PETERSEN'S ANALYSIS IN THIS CASE; HAVE YOU?

23 A NO.

24 Q NOW, THE NUMBER OF COFFEE CONSUMERS'
25 DRINKING PATTERNS THAT WERE INCLUDED IN THE NHANES FOOD
26 FREQUENCY QUESTIONNAIRE USED BY DR. PETERSEN WAS ROUGHLY
27 5,781; CORRECT?

28 A YES.

1 Q SO IT IS A SUBSTANTIALLY LARGER GROUP OF
2 CONSUMERS THAN THE DATA SET THAT YOU CHOSE TO USE FROM
3 THE N.C.A.; CORRECT?

4 A YES.

5 Q NOW, YOU HAVE ALSO OFFERED THE OPINION,
6 DR. RAPPAPORT, THAT DR. PETERSEN IMPROPERLY USED THE
7 GEOMETRIC MEAN OR THE MEDIAN AS OPPOSED TO THE ARITHMETIC
8 MEAN IN CALCULATING THE AVERAGE RATE OF INTAKE FOR THE
9 AVERAGE CONSUMER OF COFFEE; CORRECT?

10 A YES, I DID.

11 Q AND THAT CRITICISM, AGAIN, IS BASED ON YOUR
12 INTERPRETATION OF THE PROPOSITION 65 REGULATIONS;
13 CORRECT?

14 A YES.

15 Q NOW --

16 A AND I SHOULD ALSO SAY IT REFLECTS
17 DR. PETERSEN'S REPEATED USE OF THE TERM "TYPICAL" RATHER
18 THAN "AVERAGE" TO DESCRIBE HER CALCULATION.

19 Q AS YOU HAVE INDICATED, THE MEDIAN WHICH
20 REFLECTS THE 50TH PERCENTILE YOU BELIEVE IS AN IMPROPER
21 MEASURE OF CENTRAL TENDENCY IN THIS CASE AS YOU READ
22 SECTION 25721 OF THE CALIFORNIA CODE OF REGULATIONS;
23 CORRECT?

24 A YES, IN THE SENSE THAT IT DOESN'T REALLY
25 REFLECT THE AVERAGE AS IS NORMALLY INTERPRETED.

26 Q NOW, WITH RESPECT TO THE NHANES DATA, YOU
27 DID NOT REVIEW THE NHANES DATA IN TERMS OF WHETHER IT
28 PRESENTED A SKEWED DISTRIBUTION; CORRECT?

1 A I DID NOT REVIEW THE NHANES DATA.

2 Q BUT YOU DID REVIEW THE N.C.A. DATA AND YOU
3 FOUND THAT THAT WAS, IN FACT, SKEWED; CORRECT?

4 A YES.

5 Q YOU CONCLUDED THAT THE DISTRIBUTION WAS MORE
6 LOG NORMAL THAN NORMAL; CORRECT?

7 A YES, IN THE SENSE THAT THE LOG NORMAL
8 DISTRIBUTION IS A RIGHT SKEWED DISTRIBUTION AS WELL.

9 Q AND IN INSTANCES WHERE YOU HAVE A LOG NORMAL
10 DISTRIBUTION, STATISTICIANS COMMONLY WILL USE THE
11 GEOMETRIC MEAN RATHER THAN THE ARITHMETIC MEAN AS A
12 MEASURE OF CENTRAL TENDENCY; CORRECT?

13 A THEY CAN USE EITHER OR BOTH.

14 Q NOW --

15 A AND I SHOULD ALSO SAY THEY CAN USE THOSE TWO
16 MEASURES OF CENTRAL TENDENCY FOR A NORMAL DISTRIBUTION OR
17 FOR ANY OTHER DISTRIBUTION FOR THAT MATTER.

18 Q NOW, IF IT IS A COMPLETELY NORMAL
19 DISTRIBUTION, THE GEOMETRIC MEAN, THE MEDIAN, AND THE
20 ARITHMETIC MEAN WOULD BE ONE AND THE SAME; WOULD THEY
21 NOT?

22 A THEY WOULD.

23 Q IF IT WAS A PERFECT DISTRIBUTION; CORRECT?

24 A IF IT IS A SYMMETRICAL DISTRIBUTION, YES.

25 Q LET'S TALK A LITTLE BIT ABOUT N.C.A., YOUR
26 USE OF THE DATA FROM N.C.A., AND AS YOU HAVE PROVIDED TO
27 US, A TABLE THAT IS EXHIBIT 298.

28 DO YOU HAVE THAT IN FRONT OF YOU?

1 A JUST ONE MOMENT, PLEASE.

2 YES, I HAVE IT NOW, THANK YOU.

3 Q NOW, YOU RECEIVED WHAT YOU REFERRED TO AS
4 GROUP DATA THAT WAS GIVEN TO YOU BY MR. METZGER; CORRECT?

5 A YES, IT WAS -- THESE WERE SPREADSHEETS THAT
6 HAD BEEN PROVIDED FROM THE NATIONAL COFFEE ASSOCIATION TO
7 MR. METZGER, I ASSUME.

8 Q AND YOU SAY YOU ASSUME BECAUSE YOU DON'T
9 KNOW WHERE THIS CAME FROM; CORRECT?

10 A WELL, THEY -- APPARENTLY THEY MUST HAVE COME
11 FROM THE NATIONAL COFFEE ASSOCIATION BECAUSE ALL OF THE
12 SPREADSHEETS WERE LABELED WITH INFORMATION THAT WAS FROM
13 N.C.A.

14 Q DID YOU EVER SPEAK WITH ANYONE FROM N.C.A.
15 REGARDING THE COMPILATION OF DATA THAT WAS PROVIDED TO
16 YOU AND IS REFLECTED IN EXHIBIT 298?

17 A NO, I HAVE NEVER SPOKEN TO ANYONE AT N.C.A.

18 Q SO YOU DON'T KNOW WHO COMPILED THE DATA;
19 CORRECT?

20 A NO, I DON'T.

21 Q AND YOU DON'T KNOW WHAT FIRM PERFORMED THE
22 SURVEY THAT WAS THE BASIS FOR THE COLLECTING OF THE DATA
23 THAT IS REFLECTED IN EXHIBIT 298; CORRECT?

24 A NO, I DON'T.

25 Q AND YOU DON'T KNOW WHETHER THAT FIRM THAT
26 PERFORMED THE SURVEY ON BEHALF OF N.C.A. USED THIRD
27 PARTIES IN COLLECTING THE DATA; CORRECT?

28 A NO, I DON'T.

1 Q AND YOU DON'T KNOW WHETHER THE SURVEY FIRM
2 THAT PERFORMED THE SURVEY FOR THE N.C.A. USED THIRD
3 PARTIES TO VERIFY ANY OF THE RESPONSES THAT IT COMPILED
4 IN WHAT IS EXHIBIT 298; CORRECT?

5 A NO, I DON'T.

6 Q AND YOU DON'T KNOW WHETHER THE SURVEY
7 COMPANY USED THIRD PARTIES TO ANALYZE THE DATA THAT WAS
8 PUT FORWARD AND SUMMARIZED IN EXHIBIT 298; CORRECT?

9 A NO.

10 Q NOW, SO I TAKE IT YOU ARE NOT AWARE OF
11 WHETHER SURVEYS PERFORMED BY THE FIRM THAT DID THE N.C.A.
12 2013 DRINKING TRENDS SURVEY HAS EVER BEEN ADMITTED IN A
13 COURT OF LAW; CORRECT?

14 MR. SCHURZ: THE FIRM? OBJECTION. THAT IS VAGUE.

15 THE WITNESS: WOULD YOU REPEAT THE QUESTION.

16 Q BY MR. SCHURZ: YOU DON'T KNOW WHETHER ANY
17 WORK THAT WAS PERFORMED BY THE SURVEY FIRM THAT PREPARED
18 THE DATA THAT YOU ARE RELYING ON, 298, HAS EVER BEEN
19 ADMITTED IN A COURT OF LAW?

20 THE COURT: HOW WOULD HE KNOW?

21 THE WITNESS: NO, I DON'T.

22 THE COURT: WAIT A SECOND.

23 THE WITNESS: I DON'T EVEN KNOW WHICH FIRM IT IS.

24 THE COURT: HOW WOULD YOU EXPECT THIS WITNESS TO
25 ANSWER THAT QUESTION?

26 MR. SCHURZ: YOUR HONOR, THE POINT IS THIS WITNESS
27 KNOWS NOTHING ABOUT THE ORIGIN.

28 THE COURT: THE POINT IS YOU CAN ARGUE ABOUT IT.

1 YOU DON'T HAVE TO ASK THIS WITNESS. HE IS NOT A LAWYER.
2 HE DID NOT DO A STUDY OF ALL LEGAL CASES.

3 MR. SCHURZ: LET ME MOVE ON.

4 Q DR. RAPPAPORT, YOU DID NOT RECEIVE THE RAW
5 DATA FROM N.C.A.; CORRECT?

6 A THAT'S CORRECT.

7 Q WHAT YOU RECEIVED FROM MR. METZGER WAS NOT
8 THE RAW DATA; CORRECT?

9 A I STATED THAT THIS MORNING.

10 Q YOU NEVER SAW THE SCREENING SURVEY THAT WAS
11 USED BY THE N.C.A. IN PREPARING THE DATA THAT IS
12 COLLECTED HERE?

13 A NO.

14 Q SO YOU DON'T KNOW WHAT CRITERIA THAT WAS
15 USED AS TO WHO WAS INCLUDED IN THE SURVEY; CORRECT?

16 A FROM WHAT I CAN UNDERSTAND FROM READING THE
17 N.C.A. INFORMATION THAT THEY PROVIDE ON THEIR WEBSITE, IT
18 APPEARS THAT THEY HAVE A REPRESENTATIVE SAMPLE OF THE
19 U.S. POPULATION, INCLUDING COVERAGE OF MINORITY GROUPS.
20 I DON'T KNOW HOW THEY ARRIVED AT THAT REPRESENTATIVE
21 SAMPLE.

22 Q AND YOU NEVER SAW THE SCREENING SURVEY, THE
23 SET OF QUESTIONS THAT DETERMINED WHO COULD PARTICIPATE IN
24 THIS SURVEY; CORRECT?

25 A NO, I UNDERSTAND THAT AT LEAST UNTIL 2009,
26 THEY USED RANDOM DIGIT TELEPHONE DIALING TO OBTAIN THESE
27 RANDOM SURVEYS, BUT I DON'T KNOW IF THEY STILL DO THAT.

28 Q YOU DON'T KNOW HOW THE DATA WAS COLLECTED

1 FOR PURPOSES OF THE 2013 DRINKING TRENDS SURVEY; CORRECT?

2 A HOW THE DATA WERE COLLECTED?

3 Q IS IT AN ONLINE SURVEY?

4 IS IT A RANDOM DIGIT DIALING SURVEY?

5 DO YOU KNOW?

6 A IT WAS AN ONLINE SURVEY INSOFAR AS THE
7 PARTICIPATION WAS CONCERNED. HOW THE SAMPLE WAS
8 SELECTED, I DON'T KNOW WHETHER IT WAS STILL BASED ON
9 RANDOM DIGIT DIALING.

10 Q AT THE TIME OF YOUR DEPOSITION IN APRIL, YOU
11 BELIEVED IT WAS DONE BY RANDOM DIGIT DIALING; DID YOU
12 NOT?

13 A I DID BECAUSE I BASED THAT ON MY READING OF
14 THE INFORMATION THAT I HAD BEEN PROVIDED UP TO AND
15 INCLUDING 2009.

16 Q AND YOU THOUGHT --

17 MR. METZGER: COULD HE FINISH HIS ANSWER, PLEASE.

18 THE COURT: LET HIM FINISH HIS ANSWER.

19 Q BY MR. SCHURZ: I AM SORRY, DR. RAPPAPORT.

20 A I ASSUMED THAT IT HAD BEEN THE SAME IN 2013,
21 BUT SINCE THEN, I READ ADDITIONAL INFORMATION PROVIDED BY
22 N.C.A. THAT SHOWS THAT IN 2013, THE SURVEY WAS CONDUCTED
23 ONLINE.

24 Q THAT IS OUTLINED IN THE 2013 NATIONAL
25 DRINKING TRENDS SURVEY; IS IT NOT?

26 A YES, IT IS.

27 Q SO AT THE TIME OF YOUR DEPOSITION IN APRIL,
28 YOU BELIEVE THE FACT THAT IT WAS A RANDOM DIGIT DIALING

1 SURVEY WAS ONE OF ITS STRENGTHS; CORRECT?

2 A YES, I DID.

3 Q AND NOW, IN FACT, IT IS AN ONLINE SURVEY;
4 CORRECT?

5 A THE SURVEY IS CONDUCTED ONLINE. HOW THE
6 SUBJECTS ARE -- OR THE PARTICIPANTS ARE SELECTED, I DON'T
7 KNOW.

8 Q NOW, LET'S STAY WITH EXHIBIT 298 AND THE
9 GROUP DATA THAT WAS PROVIDED TO YOU.

10 YOU ARE NOT ABLE TO EVALUATE, DR. RAPPAPORT,
11 WHETHER THE GROUP DATA ACCURATELY REFLECTS THE RAW DATA;
12 CORRECT?

13 A WELL, I DID HAVE SOME INDICATION THAT THEY
14 ACCURATELY REFLECTED THE RAW DATA BECAUSE THE ESTIMATE OF
15 THE MEAN THAT THE N.C.A. HAD PROVIDED WAS 3.2 CUPS OF
16 COFFEE PER DAY, AND MINE WAS 3.08 OR SOMETHING LIKE THAT.

17 Q 3.03?

18 A 3.03, WHICH IS REASONABLE AGREEMENT
19 CONSIDERING THAT I HAD THE GROUP DATA AND I COULD NOT --
20 I HAD TO ASSUME THAT OR I DID ASSUME FOR THE PURPOSE OF
21 THAT CALCULATION THAT PEOPLE WHO HAD CONSUMED TEN OR MORE
22 CUPS OF COFFEE PER DAY CONSUMED TEN CUPS PER DAY. SO IN
23 A WAY, I WAS UNDERESTIMATING THE HIGH END OF THE
24 DISTRIBUTION.

25 Q NOW, IN REVIEWING THE GROUP DATA THAT WAS
26 COMPILED, ARE YOU AWARE OF WHETHER ANY OF THE RAW DATA
27 WAS WEIGHTED BY N.C.A. IN PREPARING THAT COMPILATION?

28 A NO, I DON'T.

1 Q ARE YOU AWARE OF N.C.A.'S WEIGHTING OF DATA
2 BASED ON AGE, GENDER OR ETHNICITY?

3 A AS FAR AS SELECTION OF PARTICIPANTS OR FOR
4 DEMOGRAPHIC PURPOSES?

5 I DON'T UNDERSTAND THE QUESTION.

6 Q FOR PURPOSES OF THE WEIGHTING OF THE DATA,
7 ARE YOU AWARE OF N.C.A.'S WEIGHTING OF THE DATA BASED ON
8 AGE, GENDER OR ETHNICITY?

9 MR. METZGER: OBJECTION; LACKING IN FOUNDATION.

10 THE COURT: OVERRULED.

11 THE WITNESS: YOU SAY "WEIGHTING OF THE DATA," SO
12 THESE WOULD BE DATA THAT HAD ALREADY BEEN COLLECTED. I
13 AM ASKING -- I AM UNSURE OF WHETHER YOU MEAN DID THEY
14 WEIGHT THE DATA IN THEIR ANALYSIS OR DID THEY WEIGHT THE
15 SAMPLING TO REFLECT CERTAIN MINORITIES AND SO ON. SO I
16 AM CONFUSED ABOUT YOUR QUESTION IN THAT SENSE.

17 Q BY MR. SCHURZ: LET'S START WITH THE FIRST
18 PIECE. ARE YOU AWARE OF WHETHER THE N.C.A. WEIGHTED THE
19 DATA THAT IT COLLECTED AS PART OF ITS ANALYSIS IN THE
20 2013 NATIONAL COFFEE DRINKING TRENDS?

21 A NO, I AM NOT.

22 Q YOU ARE NOT AWARE ONE WAY OR THE OTHER;
23 CORRECT?

24 A THAT'S CORRECT.

25 Q SO YOU ARE NOT AWARE OF WHAT FORMULA THEY
26 USED IN PERFORMING THE WEIGHTING; CORRECT?

27 A NO.

28 Q ALL RIGHT. SO IN THIS CASE, HOW WAS THE

1 DATA COLLECTED THAT IS PART OF YOUR EXHIBIT 298?

2 A HOW DID THE PARTICIPANTS RESPOND TO THE
3 SURVEY OR --

4 Q HOW DID THE N.C.A. COLLECT THE DATA, THE RAW
5 DATA, AND SUMMARIZE IT IN THE COMPILATION OF DATA THAT
6 YOU HAVE INDICATED AT SECTION 298?

7 A WHAT N.C.A. STATES IS THAT THEY OBTAINED A
8 REPRESENTATIVE SAMPLE OF THE U.S. POPULATION, MINDFUL OF
9 INCLUDING MINORITY GROUPS. THAT IS WHAT THEY SAY. IT IS
10 A REPRESENTATIVE SAMPLE. HOW EXACTLY THEY ARRIVED AT
11 THAT REPRESENTATIVE SAMPLE, I DON'T KNOW.

12 Q YOU DON'T KNOW WHO COLLECTED THE DATA;
13 CORRECT?

14 A FOR THE N.C.A., NO, I DON'T.

15 Q YOU DON'T KNOW HOW IT WAS TRANSPOSED;
16 CORRECT?

17 A NO. I THINK I HAVE ALREADY SAID ALL THIS
18 BEFORE.

19 Q ALL RIGHT. NOW, WAS THE METHODOLOGY FOR THE
20 DATA COLLECTION THAT IS INCLUDED IN EXHIBIT 298
21 VALIDATED?

22 A VALIDATED IN WHAT SENSE?

23 Q WAS THE SURVEY METHODOLOGY, WHICH BECAME THE
24 BASIS FOR THE DATA THAT IS COLLECTED AND SUMMARIZED IN
25 SECTION 298, WAS IT VALIDATED?

26 A YOU WILL HAVE TO INTERPRET WHAT YOU MEAN BY
27 "VALIDATED."

28 Q YOU ARE FAMILIAR WITH SURVEYS BEING

1 VALIDATED?

2 A I AM FAMILIAR WITH -- I SEE WHAT YOU MEAN.
3 WAS IT VALIDATED?

4 NO, I DON'T KNOW.

5 Q DO YOU KNOW HOW THEY WENT ABOUT VERIFYING
6 RESPONSES TO DETERMINE THAT THEY WERE, IN FACT, THE
7 PARTICIPANTS WHO INDICATED THAT THEY WERE RESPONDING
8 ONLINE?

9 A NO, I DON'T.

10 Q AND DO YOU KNOW WHAT PERCENTAGE OF THE
11 RESPONSES WERE VERIFIED, IF ANY?

12 A NO, I DON'T.

13 Q DR. RAPPAPORT, AS A SCIENTIST, DO YOU RELY
14 ON DATA COLLECTED BY UNKNOWN THIRD PARTIES IN DEVELOPING
15 SCIENTIFIC OPINIONS?

16 A IT DEPENDS. IN THE CASE OF THE N.C.A.,
17 THESE ARE DATA THAT ARE COLLECTED FOR DETERMINING TRENDS
18 IN COFFEE CONSUMPTION ACROSS THE U.S. THESE SURVEYS HAVE
19 BEEN GOING ON FOR MORE THAN 50 YEARS. THEY ARE
20 COMPLETELY FINANCED, AS I UNDERSTAND, BY THE COFFEE
21 INDUSTRY, WHO, I WOULD HAVE TO THINK, WOULD BE VERY
22 INTERESTED IN OBTAINING UNBIASED DATA FOR THEIR
23 PARTICIPANT COMPANIES TO USE.

24 AS I MENTIONED THIS MORNING, SIMILAR
25 ANALYSES HAVE BEEN PERFORMED BY AT LEAST TWO OTHER
26 SCIENTIFIC GROUPS THAT I AM AWARE OF IN TRYING TO
27 EVALUATE COFFEE CONSUMPTION.

28 Q NOW --

1 MR. METZGER: HOLD ON. HE HASN'T FINISHED. LET
2 HIM FINISH HIS ANSWER.

3 THE COURT: LET THE WITNESS FINISH HIS ANSWER.

4 THE WITNESS: SO I DON'T THINK IT IS COMPLETELY
5 UNPRECEDENTED FOR SCIENTISTS TO USE DATA FROM N.C.A. IN
6 MAKING THESE KIND OF EVALUATIONS.

7 Q BY MR. SCHURZ: NOW, THE F.D.A. REPORT THAT
8 YOU REFERENCED, YOU DID NOT INCLUDE THAT IN YOUR RELIANCE
9 MATERIALS; CORRECT?

10 A NO, I HAD READ IT, BUT I DID NOT INCLUDE IT
11 IN THE MATERIALS THAT WE DISCUSSED IN THE DEPOSITION.

12 Q AND YOU NEVER MENTIONED IT IN THE
13 DEPOSITION; DID YOU?

14 A I DID NOT.

15 Q WITH RESPECT TO THE IARC MONOGRAPH AS
16 UNDISCLOSED, YOU DID NOT PRODUCE THAT EITHER IN YOUR
17 RELIANCE MATERIALS; CORRECT?

18 A NO, I DID NOT.

19 Q NOR DID YOU REFERENCE IT AT THE TIME OF YOUR
20 DEPOSITION IN APRIL; DID YOU?

21 A THAT'S CORRECT.

22 Q NOW, AMONG YOUR CRITICISMS OF THE NHANES
23 SURVEY IS THAT YOU BELIEVE IT IS TOO COMPLICATED; IS THAT
24 CORRECT?

25 A IN THE SENSE THAT IT INCLUDES ALL --
26 ESSENTIALLY ALL FOOD CATEGORIES, IT IS NOT FOCUSED ONLY
27 ON COFFEE.

28 Q AND YOU SEE THAT AS A LIABILITY; CORRECT?

1 A IN THE SENSE THAT IT MAKES IT MORE DIFFICULT
2 TO COLLECT THE DATA INITIALLY, AND ALSO TO REALLY USE THE
3 DATA, I THINK, IN A FOCUSED ANALYSIS SUCH AS THE ONE WE
4 ARE INTERESTED IN HERE.

5 Q NOW, YOU BASE PART OF YOUR CRITICISMS ON THE
6 NHANES FOOD FREQUENCY QUESTIONNAIRE BECAUSE IT INCLUDED
7 WHAT YOU DENOMINATE AS THOUSANDS OF QUESTIONS; CORRECT?

8 A I MAY HAVE SAID THOUSANDS OF QUESTIONS. I
9 AM NOT SURE OF THE EXACT NUMBER, BUT THERE ARE A LOT OF
10 QUESTIONS.

11 Q HOW MANY QUESTIONS ARE THERE IN THE NHANES
12 FOOD FREQUENCY QUESTIONNAIRE?

13 A I JUST SAID I DON'T KNOW.

14 Q YOU DON'T HAVE ANY INDICATION, ANY ESTIMATE
15 OF HOW MANY QUESTIONS ARE IN THE NHANES FOOD FREQUENCY
16 QUESTIONNAIRE?

17 A NO.

18 Q WITH RESPECT TO THE N.C.A. DATABASE THAT YOU
19 RELY ON, HOW MANY QUESTIONS ARE IN THE N.C.A. SURVEY?

20 A WELL, I AM NOT SURE. BASED UPON THE
21 SPREADSHEETS THAT I HAVE, I WOULD SAY THAT IT WAS
22 SOMEWHERE IN THE NEIGHBORHOOD OF 100. I AM NOT SURE.

23 Q DO YOU KNOW WHETHER THE N.C.A. SURVEY HAS
24 MORE QUESTIONS AND IS MORE COMPLICATED THAN THE NHANES
25 SURVEY?

26 A I DON'T KNOW, BUT MY OPINION IS THAT IT IS
27 PROBABLY LESS COMPLICATED BECAUSE IT IS FOCUSED ON A
28 SINGLE COMMODITY.

1 Q BUT YOU HAVE NEVER ACTUALLY SEEN THE N.C.A.
2 QUESTIONNAIRE; CORRECT?

3 A I HAVE NOT SEEN THE ENTIRE QUESTIONNAIRE,
4 NO.

5 Q SO YOUR OPINION IS NOT BASED UPON A REVIEW
6 OR A COMPARISON OF THE NHANES QUESTIONNAIRE VERSUS THE
7 N.C.A. QUESTIONNAIRE; CORRECT?

8 A CORRECT.

9 Q DO YOU HAVE ANY BACKGROUND IN ONLINE
10 SURVEYS?

11 A NO.

12 Q AND DO YOU HAVE ANY UNDERSTANDING OF THE
13 CHALLENGES WITH RESPECT TO CONDUCTING AN ONLINE SURVEY?

14 A NO.

15 Q NOW, TURNING TO A NEW TOPIC, DR. RAPPAPORT.
16 YOU HAVE NO OPINION ABOUT HOW MUCH COFFEE IS IN A CUP;
17 CORRECT?

18 A NO, I HAVE NO OPINION REGARDING THE AMOUNT
19 OF COFFEE IN A CUP.

20 Q ALL RIGHT. LET'S SWITCH GEARS IF WE CAN AND
21 DISCUSS SOME OF THE OPINIONS THAT YOU OFFERED WITH
22 RESPECT TO THE TOXICOKINETICS OF ACRYLAMIDE. THIS WAS
23 THE FIRST HALF OF YOUR TESTIMONY.

24 YOU INDICATED, DR. RAPPAPORT, THAT A BROAD
25 RANGE OF FOODS INCLUDE ACRYLAMIDE; CORRECT?

26 A YES.

27 Q IT INCLUDES BOTH COOKED FOODS AND SOME
28 NON-COOKED FOODS; CORRECT?

1 A I AM ONLY AWARE OF FOODS THAT HAVE BEEN --
2 OR FOOD ITEMS THAT HAVE BEEN HEATED AS CONTRIBUTING TO
3 ACRYLAMIDE. THERE COULD BE SOME FOODS THAT HAVE
4 ACRYLAMIDE NATURALLY. I AM NOT SURE OF THAT.

5 Q OKAY. NOW, THE FOODS THAT YOU REFERENCE
6 WOULD INCLUDE POTATO PRODUCTS AS YOU HAVE INDICATED;
7 CORRECT?

8 A YES.

9 Q IT WOULD INCLUDE READY-TO-EAT BREAKFAST
10 CEREALS, BREADS AND BAKED GOODS; CORRECT?

11 A YES.

12 Q AND IN THE UNITED STATES, THE CONTRIBUTION
13 OF COFFEE IS RELATIVELY LITTLE TO THE AVERAGE DAILY
14 ACRYLAMIDE INTAKE; CORRECT?

15 IT IS APPROXIMATELY SEVEN PERCENT; IS THAT
16 CORRECT?

17 A I HAVE NEVER INVESTIGATED THE INTAKE FROM
18 COFFEE IN THE U.S. POPULATION.

19 Q WELL, YOU CITE AT SLIDE NUMBER 20 THE DYBING
20 ARTICLE, AND THIS IS ONE OF THE ARTICLES THAT YOU RELIED
21 ON; CORRECT?

22 PLAINTIFF'S EXHIBIT 00929; CORRECT?

23 A YES.

24 Q DID YOU REVIEW THAT ARTICLE?

25 A I DID.

26 Q ARE YOU FAMILIAR WITH THAT ARTICLE'S
27 ESTIMATE OF THE CONTRIBUTION OF COFFEE IN THE AMERICAN
28 DIET?

1 A I REMEMBER THAT THEY DISCUSSED IT, BUT I DID
2 NOT PAY PARTICULAR ATTENTION TO IT.

3 Q STAYING WITH THE SLIDE NUMBER 20, YOU ALSO
4 CITE AN ARTICLE BY XU, PROFESSOR XU. X-U.

5 DO YOU SEE THAT?

6 A YES.

7 Q NOW, THAT ARTICLE IS PX-02221. IF I COULD
8 ASK YOU TO TAKE A LOOK AT IT, I JUST HAVE A COUPLE OF
9 QUESTIONS ABOUT YOUR RELIANCE ON THE DOCUMENT.

10 DO YOU HAVE EXHIBIT 2221 IN FRONT OF YOU,
11 DR. RAPPAPORT?

12 A YES.

13 Q THIS IS ONE OF THE DOCUMENTS YOU RELIED ON;
14 CORRECT?

15 A YES.

16 Q IN FACT, IN YOUR RELIANCE MATERIALS, YOU
17 IDENTIFY A GROUP OF 18 ARTICLES THAT CONSTITUTE RELIANCE
18 MATERIALS THAT YOU ARE OFFERING FOR YOUR OPINIONS
19 RELATING TO THE TOXICOKINETICS OF ACRYLAMIDE; IS THAT
20 RIGHT?

21 A I HAVE NOT COUNTED THEM.

22 Q LET'S STAY WITH PROFESSOR XU'S ARTICLE HERE.
23 NOW, THIS ARTICLE WAS TO BE PUBLISHED -- IS
24 TO BE PUBLISHED THIS YEAR; CORRECT?

25 A IT WAS, I THINK, IN PRESS WHEN I REVIEWED
26 IT. IT IS OBVIOUSLY NOT IN FINAL FORM HERE.

27 Q THE ARTICLE, IF I COULD TURN YOUR ATTENTION
28 TO 2221-005, THE ARTICLE DENOMINATES WHAT IT IDENTIFIES

1 AS CRITICAL ISSUES OF ACRYLAMIDE WITH A FOCUS ON RISK
2 ASSESSMENT.

3 DO YOU SEE THAT?

4 A ON PAGE 005?

5 Q YES. RIGHT ABOVE THE PARAGRAPH THAT READS,
6 ARABIC 2, "ACRYLAMIDE FORMATION."

7 DO YOU SEE THAT?

8 AT THE PRECEDING PARAGRAPH, IT READS:
9 THIS -- "THE REVIEW ADDRESSES SOME CRITICAL ISSUES OF
10 ACRYLAMIDE WITH A FOCUS ON RISK ASSESSMENT."

11 DO YOU SEE THAT?

12 A I DO.

13 Q NOW, THE AUTHORS EVALUATE THE STATE OF THE
14 EPIDEMIOLOGIC LITERATURE ON DIETARY AND OCCUPATIONAL
15 EXPOSURES; CORRECT?

16 A THEY DISCUSS IT, YES.

17 Q AND THEY CONCLUDE, DO THEY NOT, THAT SO FAR
18 THE EPIDEMIOLOGICAL STUDIES DO NOT SUGGEST A CLEAR
19 ASSOCIATION OF CANCER WITH DIETARY OR OCCUPATIONAL
20 EXPOSURE TO ACRYLAMIDE; CORRECT?

21 A THEY DO SAY THAT.

22 Q NOW, THE XU ARTICLES CONCLUDE -- AND IF I
23 COULD DIRECT YOUR ATTENTION TO PAGE 9, WHAT IS 2221-009,
24 THE FIRST FULL PARAGRAPH, SECOND SENTENCE.

25 LET ME KNOW WHEN YOU HAVE THAT IN FRONT OF
26 YOU.

27 A STARTING "CURRENT EPIDEMIOLOGICAL," THAT
28 SENTENCE?

1 Q YES. WE CAN START WITH THE EARLIER SENTENCE
2 WHERE IT READS, "FROM AN EPIDEMIOLOGICAL POINT OF VIEW,
3 NO CONVINCING RELATIONSHIP BETWEEN ACRYLAMIDE EXPOSURE
4 AND TUMOR FORMATION HAS BEEN ESTABLISHED."

5 DO YOU SEE THAT?

6 A I SEE THAT, BUT I WAS NOT ASKED TO REVIEW
7 THE EPIDEMIOLOGY OF ACRYLAMIDE. I WAS ASKED TO LOOK AT
8 THE TOXICOKINETICS RELATED TO ACRYLAMIDE.

9 Q AND AMONG THE 18 DOCUMENTS YOU IDENTIFIED AS
10 YOUR RELIANCE MATERIALS, THIS WAS ONE; CORRECT?

11 A THIS WAS ONE, BUT I DID NOT RELY ON
12 INFORMATION ABOUT RISK ASSESSMENT OR EPIDEMIOLOGY FOR THE
13 PURPOSE OF MY REVIEW. I MEAN, THIS ARTICLE ALSO CONTAINS
14 INFORMATION THAT IS RELEVANT TO TOXICOKINETICS.

15 Q YOU RELIED ON THIS ARTICLE BECAUSE YOU
16 BELIEVED IT WAS A REASONABLE ARTICLE TO FORM AN OPINION
17 ON; CORRECT?

18 A IT WAS A REVIEW ARTICLE, AND IT DID INCLUDE
19 REASONABLE INFORMATION THAT PROVIDED THE BASIS OF MY
20 OPINIONS, BUT MY OPINIONS DID NOT FOCUS ON EPIDEMIOLOGY
21 OR RISK ASSESSMENT.

22 Q I UNDERSTAND. NOW, THE NEXT SENTENCE HERE
23 THAT WE ARE LOOKING AT IN YOUR RELIANCE MATERIALS OF THE
24 XU AUTHORS INCLUDE: "CURRENT EPIDEMIOLOGICAL AND
25 TOXICOLOGICAL EVIDENCE IS INSUFFICIENT TO INDICATE THAT
26 THE AMOUNT OF ACRYLAMIDE CONSUMED IN THE NORMAL DIET ARE
27 LIKELY TO RESULT IN ADVERSE HUMAN HEALTH EFFECTS,
28 PARTICULARLY CANCER."

1 DO YOU SEE THAT?

2 A I SEE IT.

3 MR. METZGER: EXCUSE ME, YOUR HONOR. THE ENTIRE
4 SENTENCE SHOULD BE READ RATHER THAN JUST --

5 THE COURT: WHAT IS THE DIFFERENCE?

6 THE WITNESS SAID HE DID NOT RELY ON THIS
7 ANYWAY. SO WE ARE JUST SPINNING WHEELS HERE.

8 MR. METZGER: WE ARE, BUT IF HE IS GOING TO READ
9 FROM AN ARTICLE, AT LEAST, FOR PURPOSES OF COMPLETION,
10 HAVE THE ENTIRE SENTENCE BE READ.

11 THE COURT: COUNSEL CAN READ, WE CAN HAVE
12 RESPONSIVE READINGS BACK AND FORTH. I DON'T THINK IT
13 GOES ANYPLACE.

14 MR. METZGER: ALL RIGHT. YOU ARE THE TRIER OF
15 FACT. I WILL SIT DOWN, AS I AM.

16 Q BY MR. SCHURZ: YOU RELIED ON THIS ARTICLE
17 BY PROFESSOR XU; CORRECT?

18 A WELL, I RELIED ON IT TO THE EXTENT THAT IT
19 FORMED THE BASIS OF MY OPINIONS, BUT MY OPINIONS DID NOT
20 FOCUS ON EITHER THE EPIDEMIOLOGY OR THE TOXICOLOGY OR THE
21 RISK ASSESSMENT.

22 Q NOW, TURNING TO SLIDE NUMBER 24 THAT WE TOOK
23 A LOOK AT THIS MORNING, THERE WAS SOME DISCUSSION ABOUT
24 THE FOLLOWING: ORAL DOSING OF ACRYLAMIDE AND ITS
25 DISPERSION IN THE BODY.

26 DO YOU RECALL THAT DISCUSSION YOU HAD WITH
27 MR. METZGER?

28 A YES, YOU MIGHT REFRESH MY MEMORY ABOUT YOUR

1 POINT, I AM NOT SURE.

2 Q WELL, THERE WERE A SERIES OF QUESTIONS THAT
3 SAID TO THE EFFECT THAT IT WAS ABSORBED FROM ORAL DOSING
4 AND IT IS METABOLIZED AND DISTRIBUTED TO ALL PARTS OF THE
5 BODY; CORRECT?

6 A YES.

7 Q WHAT WE WERE TALKING ABOUT HERE IS THE
8 BODIES OF RATS AND MICE; CORRECT?

9 A YES.

10 Q AND SPECIFICALLY, WHAT WE ARE TALKING ABOUT
11 IN SLIDE NUMBER 24 IS THE ABSORPTION FROM ORAL DOSING IN
12 RATS AND MICE; CORRECT?

13 A YES.

14 Q AND ALL OF THE AUTHORITIES THAT ARE CITED ON
15 SLIDE NUMBER 24 RELATE TO RATS, FISCHER RATS AND MICE;
16 CORRECT?

17 A YES, THEY DO.

18 Q LET'S TALK A MOMENT ABOUT THE FENNEL
19 DECISION THAT YOU DISCUSSED AGAIN THIS MORNING WITH
20 MR. METZGER AND AS PART OF YOUR RELIANCE MATERIAL.

21 MR. METZGER: THE FENNEL ARTICLE OR DECISION?

22 MR. SCHURZ: STUDY.

23 THE WITNESS: THE FENNEL 2005 PAPER?
24 BY MR. SCHURZ:

25 Q YES. YOU WERE LOOKING AT THIS ARTICLE TO
26 EVALUATE SYSTEMIC DOSES FOR HUMANS VERSUS RATS; CORRECT?

27 A I WAS MAINLY RELYING ON IT TO EVALUATE THE
28 DOSE IN HUMANS.

1 Q WHAT FENNEL CONCLUDED WAS THAT PEOPLE
2 METABOLIZE ACRYLAMIDE TO GLYCIDAMIDE AT A LESSER EXTENT
3 THAN RODENTS; CORRECT?

4 A HE MAY HAVE SAID THAT, YES.

5 Q NOW --

6 A BUT I SHOULD ADD THAT IN AN ANALYSIS OF
7 THESE DATA BY VIKSTROM THAT I ALSO USED AS ONE OF MY
8 REFERENCES, THEY LOOK CAREFULLY AT THE FENNEL DATA,
9 ALONG WITH ALL OTHER DATA FOR THAT MATTER IN RATS AND
10 HUMANS, AND THEY HAD MORE UP-TO-DATE INFORMATION ABOUT
11 SYSTEMIC DOSE BASED UPON THE HEMOGLOBIN ADDUCT LEVELS
12 THAT WERE AVAILABLE TO FENNEL AT THE TIME. THEY
13 CONCLUDED THAT HUMANS, IN FACT, HAVE HIGHER DOSES THAN
14 RATS.

15 Q LET'S FOCUS ON FENNEL. WE WILL GET TO
16 VIKSTROM.

17 A OKAY.

18 Q SO, NOW, WHAT FENNEL CONCLUDED WAS THAT
19 HUMANS METABOLIZE ACRYLAMIDE VIA GLYCIDAMIDE TO A LESSER
20 EXTENT THAN RODENTS; CORRECT?

21 A I WOULD LIKE TO SEE THE STATEMENT THAT HE
22 MADE.

23 Q SURE. LET ME SHOW YOU WHAT IS DX-10286. IS
24 THIS THE 2005 ARTICLE THAT YOU ARE RELYING ON?

25 A YES.

26 Q I DIRECT YOUR ATTENTION TO THE LAST SENTENCE
27 IN THE ABSTRACT, ON THE FIRST PAGE OF DX-10286, WHERE THE
28 AUTHORS STATE, QUOTE "THIS STUDY INDICATED THAT HUMANS

1 METABOLIZE ACRYLAMIDE VIA GLYCIDAMIDE TO A LESSER EXTENT
2 THAN RODENTS."

3 DO YOU SEE THAT?

4 A YES.

5 Q NOW, WHAT FENNELLS WAS INTERESTED IN IN THIS
6 STUDY WAS EVALUATING AND OBSERVING HOW CONVERSION RATES
7 MIGHT BE SEEN IN URINARY METABOLITES; CORRECT?

8 A YES.

9 Q SO THE EXERCISE HERE WAS TO EVALUATE THE
10 URINE OF THESE ANIMALS AND TO THEN MAKE A DETERMINATION,
11 BASED UPON THE METABOLITES, AS TO THE CONVERSION RATES OF
12 ACRYLAMIDE TO GLYCIDAMIDE; CORRECT?

13 A YES.

14 Q OKAY. NOW, WHAT FENNELLS FOUND WAS THAT THE
15 METABOLISM VIA GLYCIDAMIDE WAS AT 12 PERCENT. METABOLISM
16 VIA GLYCIDAMIDE DERIVED FROM GLYCIDAMIDE AND GLYCERAMIDE
17 IN HUMANS WAS APPROXIMATELY 12 PERCENT OF THE TOTAL
18 URINARY METABOLITE; CORRECT?

19 A WHERE DO YOU SEE THAT?

20 Q I AM ON DX-10286-0010, ON THE LEFT-HAND
21 COLUMN, THREE FULL PARAGRAPHS DOWN. IT IS HIGHLIGHTED
22 HERE ON YOUR SCREEN.

23 A YES, HE SAYS THAT.

24 Q AND OF THAT 12 PERCENT, ROUGHLY 11 PERCENT
25 WAS ASSOCIATED WITH GLYCIDAMIDE HYDROLYSIS OR
26 GLYCERAMIDE; RIGHT?

27 A YES.

28 Q GLYCERAMIDE IS NOT REACTIVE; CORRECT?

1 A IT IS NOT REACTIVE?

2 I MEAN, IN THE SENSE THAT IT IS NOT TOXIC OR
3 WHAT?

4 Q DOES NOT BIND WITH D.N.A.; CORRECT?

5 A NO, NOT TO MY KNOWLEDGE.

6 Q SO WHAT FENNELLS SUGGESTS THEN IS AT LEAST
7 WITH RESPECT TO THE URINARY METABOLITES THAT IT IS
8 LOOKING AT, 12 PERCENT IS METABOLIZED TO GLYCIDAMIDE
9 OR GLYCERAMIDE AND OF THAT 12 PERCENT, 11 PERCENT IS
10 ASSOCIATED WITH GLYCERAMIDE; RIGHT?

11 A THIS IS URINARY EXCRETION; CORRECT?

12 Q CORRECT.

13 A BUT ALL OF THE GLYCERAMIDE IS DERIVED FROM
14 GLYCIDAMIDE.

15 Q I UNDERSTAND THAT.

16 MR. METZGER: HAVE YOU FINISHED, DR. RAPPAPORT?

17 THE WITNESS: SO ALL OF THE DOSE OF GLYCERAMIDE
18 REFLECTS THE INITIAL PRODUCTION OF GLYCIDAMIDE. IT IS A
19 HYDROLYSIS PRODUCT OF GLYCIDAMIDE. THAT IS WHY IT IS
20 EXCRETED IN THE URINE.

21 Q BY MR. SCHURZ: THE FENNELLS AUTHORS FURTHER
22 CONCLUDED THAT THE RATE AT WHICH PEOPLE METABOLIZE
23 GLYCIDAMIDE IS CONSIDERABLY LOWER THAN THE RATE OF
24 METABOLISM IN RATS; CORRECT?

25 A YES, THEY CONCLUDED THAT ON THE BASIS OF THE
26 URINARY METABOLITES.

27 Q THAT THE RATS WERE MORE THAN DOUBLE THE RATE
28 OF PEOPLE, CORRECT, AS MEASURED BY FENNELLS IN THIS STUDY?

1 A YES, BUT IT IS VERY DIFFICULT TO BASE THESE
2 ARGUMENTS SOLELY ON URINARY METABOLITES.

3 Q IT IS YOUR ARTICLE, NOT MINE.

4 THE COURT: LET THE WITNESS FINISH HIS ANSWER.

5 THE WITNESS: I THINK A BETTER WAY OF GETTING AN
6 ESTIMATE OF THE GLYCIDAMIDE DOSE, WHICH IS REALLY WHAT WE
7 ARE AFTER HERE, IS THE USE OF THE HEMOGLOBIN ADDUCTS,
8 WHICH, OF COURSE, FENNELLS WAS INTERESTED IN AS WELL.
9 THIS IS THE WORK THAT I REFERRED TO FROM VIKSTROM WHERE
10 THEY INVESTIGATED THIS ARTICLE FROM FENNELLS AND OTHER
11 ARTICLES, AND PLUS THEIR OWN WORK, AND MADE THE
12 CONCLUSION THAT, IN FACT, HUMANS PRODUCE MORE GLYCIDAMIDE
13 PER UNIT OF DOSE THAN THE RATS DO. ABOUT TWICE AS MUCH.

14 THE COURT: HAVE YOU COMPLETED YOUR ANSWER?

15 THE WITNESS: YES, I AM FINISHED, YOUR HONOR.

16 THE COURT: NEXT QUESTION.

17 Q BY MR. SCHURZ: IN TERMS OF THE URINARY
18 METABOLITES, WHAT THE FENNELLS AUTHORS CONCLUDED IS THAT
19 HUMANS METABOLIZE GLYCIDAMIDE AT A RATE SIGNIFICANTLY
20 LOWER THAN RATS AND MICE; CORRECT?

21 A THAT WAS THEIR CONCLUSION.

22 Q AND THAT THE RATS METABOLIZE GLYCIDAMIDE AT
23 A RATE OF 28 PERCENT AND MICE AT 59 PERCENT; CORRECT?

24 A YES.

25 Q AND HUMANS AT 12 PERCENT; CORRECT?

26 A YES, BUT AGAIN, I MUST SAY THAT IT IS
27 DIFFICULT TO BASE THESE KINDS OF ANALYSES ON MEASUREMENTS
28 OF THESE URINARY METABOLITES BECAUSE THE PATTERNS OF

1 PRODUCTION OF URINARY METABOLITES IN HUMANS, RATS AND
2 MICE ARE DIFFERENT. YOU HAVE TO ACCOUNT FOR EVERYTHING.
3 IF YOU ARE MISSING SOMETHING, IT IS NOT GOING TO ADD UP
4 IN YOUR BALANCE HERE. SO IT IS MORE DIFFICULT. THAT IS
5 WHY I AM SAYING THAT RELYING ON THE HEMOGLOBIN ADDUCTS
6 FOR THIS KIND OF A CALCULATION SHOULD BE BETTER.

7 Q NOW, THE FENNELLS STUDY DID NOT TEST FOR
8 D.N.A. ADDUCTS IN HUMAN SUBJECTS; DID IT?

9 A NO, I DON'T THINK IT DID.

10 Q NOW, LET'S TURN TO THE VIKSTROM STUDY.

11 THE COURT: WE ARE GOING ON TO ANOTHER STUDY. WE
12 WILL TAKE A RECESS AT THIS TIME FOR 15 MINUTES.

13
14 (RECESS TAKEN.)

15
16 THE COURT: BACK ON THE RECORD IN CERT VERSUS
17 STARBUCKS. ALL COUNSEL ARE PRESENT. DR. RAPPAPORT IS ON
18 THE STAND.

19 THE CLERK: ONCE AGAIN, SIR, YOU HAVE PREVIOUSLY
20 BEEN SWORN. STATE YOUR NAME AGAIN FOR THE RECORD.

21 THE WITNESS: STEVEN RAPPAPORT.

22 THE COURT: MR. SCHURZ WAS INQUIRING. COUNSEL MAY
23 PROCEED.

24 MR. SCHURZ: THANK YOU YOUR HONOR.

25 Q GOOD AFTERNOON, DR. RAPPAPORT.

26 A GOOD AFTERNOON.

27 Q WE WERE DISCUSSING THE FENNELLS PAPER, ONE OF
28 YOUR RELIANCE MATERIALS BEFORE OUR BREAK, AND ONE FINAL

1 QUESTION: THE SUBJECTS IN FENNEL WERE FED ACRYLAMIDE,
2 PURE ACRYLAMIDE; CORRECT?

3 A YES, C-13 LABELED ACRYLAMIDE.

4 Q IT WAS NOT PART OF A DIETARY MATRIX OR
5 ACRYLAMIDE IN FOOD, IT WAS STRAIGHT ACRYLAMIDE; CORRECT?

6 A IT WAS ADMINISTERED IN DRINKING WATER, SO,
7 IN A SENSE, IT WAS DIETARY.

8 THE COURT: IT WAS ADMINISTERED HOW?

9 THE WITNESS: IN DRINKING WATER.

10 THE COURT: IS ACRYLAMIDE LIQUID, SOLID OR GAS?
11 WHAT IS ACRYLAMIDE?

12 THE WITNESS: IT IS A LIQUID, YOUR HONOR. IT IS
13 VERY SOLUBLE IN WATER.

14 Q BY MR. SCHURZ: LET'S TALK A LITTLE BIT
15 ABOUT THE VIKSTROM PAPER WHICH YOU HAVE REFERENCED A
16 NUMBER OF TIMES. IT IS IDENTIFIED IN SLIDE NUMBER 32 OF
17 YOUR PAPERS.

18 NOW, THE VIKSTROM PAPER DID NOT REPORT
19 D.N.A. ADDUCTS IN ITS HUMAN VOLUNTEERS; DID IT?

20 A NO, IT DID NOT.

21 Q NOW, WE WERE TALKING EARLIER THIS MORNING
22 ABOUT ADDUCTS AS MARKERS OF EXPOSURE AS OPPOSED TO
23 MARKERS OF GENETIC DAMAGE; CORRECT?

24 A I INDICATED THAT THERE WERE BIOMARKERS OF
25 EXPOSURE AND THERE WERE BIOMARKERS OF GENETIC DAMAGE.
26 HEMOGLOBIN ADDUCTS WOULD DEFINITELY BE BIOMARKERS OF
27 EXPOSURE. D.N.A. ADDUCTS ARE IN A GRAY AREA. THEY COULD
28 BE USED AS MEASURES OF EXPOSURE. THEY COULD BE USED AS

1 MEASURES OF GENOTOXICITY BECAUSE THAT IS THE ORIGIN OF
2 GENOTOXICITY IS REACTION TO D.N.A.

3 Q THE VIKSTROM PAPER DID NOT REPORT ANY D.N.A.
4 ADDUCTS IN ITS HUMAN VOLUNTEERS; RIGHT?

5 A THAT'S CORRECT.

6 Q AND, IN FACT, THERE HAVE NOT BEEN ANY
7 PUBLISHED REPORTS ON IN VIVO MEASUREMENT IN HUMANS OF
8 D.N.A. ADDUCTS FROM ACRYLAMIDE EXPOSURE; ISN'T THAT
9 CORRECT?

10 A NOT TO MY KNOWLEDGE.

11 Q NOW, RETURNING TO THE VIKSTROM PAPER,
12 VIKSTROM REPORTED THE RESULTS OF PEOPLE EXPOSED TO
13 ACRYLAMIDE RICH-FOODS; IS THAT CORRECT?

14 A YES.

15 Q THE FOODS THAT WERE THE FOCUS OF THE STUDY
16 WERE POTATOES AND BREAD; CORRECT?

17 A YES, PRIMARILY.

18 Q AND THE STUDIES REPORTED IN THE VIKSTROM
19 PAPER DID NOT MEASURE EXPOSURES TO COFFEE; CORRECT?

20 A NOT THAT I RECALL, NO.

21 Q IN VIKSTROM, NO EFFORT WAS MADE TO IDENTIFY
22 THE CONTRIBUTION OF PRE-EXPOSURE HEMOGLOBIN ADDUCTS IN
23 THE BASELINE TO INDIVIDUAL FOODS; IS THAT CORRECT?

24 A NO.

25 Q NOW, LET'S TALK A LITTLE BIT ABOUT THE
26 ZEIGER AND ABRAMSSON PAPERS THAT YOU DISCUSSED AT SOME
27 LENGTH THIS MORNING WITH MR. METZGER.

28 NOW, AS A PRELIMINARY MATTER, DR. RAPPAPORT,

1 YOU ARE NOT AN EXPERT IN THE SELECTION OF MODELS;
2 CORRECT?

3 A SELECTION OF MODELS?

4 Q YOU ARE NOT AN EXPERT IN THE SELECTION OF
5 MODELS IN THE RISK ASSESSMENT CONTEXT; CORRECT?

6 A NO, NOT FOR RISK ASSESSMENT.

7 Q AND YOU HAVE NO EXPERIENCE WITH THE
8 LINEARIZED MULTISTAGE MODEL; CORRECT?

9 A I KNOW WHAT IT IS. I AM FAMILIAR WITH IT.

10 Q BUT YOU HAVE NOT USED IT; CORRECT?

11 A NO, I HAVE NOT.

12 Q SO, NOW, YOU MENTIONED IN YOUR DISCUSSION
13 THIS MORNING WITH MR. METZGER IN YOUR DISCUSSION ABOUT
14 THE ZEIGER AND ABRAMSSON-ZETTERBERG PAPERS THAT IT IS
15 IMPORTANT TO LOOK AT THE TOTALITY OF THE EVIDENCE IN
16 TERMS OF YOUR EVALUATION OF THE LINEARITY OF
17 TOXICOKINETIC PROCESSES; CORRECT?

18 A I THINK I REFERRED TO THE TOTALITY OF THE
19 DATA.

20 Q AND IN THIS CASE, YOU ARE LOOKING AT THE
21 ZEIGER STUDY AND THE ABRAMSSON-ZETTERBERG STUDY; CORRECT?

22 A YES.

23 Q IN BOTH OF THESE CASES, THESE INVOLVED
24 ANIMALS; RIGHT?

25 A YES.

26 Q THE ABRAMSSON STUDY INVOLVED A STUDY OF FIVE
27 MICE PER DOSE GROUP FOR A TOTAL OF 35 MICE IN THAT STUDY;
28 CORRECT?

1 A YES.

2 Q AND THE ZEIGER PAPER RELIED ON TEN MICE PER
3 DOSE GROUP WITH MORE DOSE GROUPS, AND IT WAS ROUGHLY 120
4 MICE; CORRECT?

5 A YES. I CANNOT REMEMBER THE EXACT NUMBER OF
6 DOSE GROUPS.

7 Q AND YOU PLACED GREATER WEIGHT ON THE ZEIGER
8 STUDY THAN THE ABRAMSSON STUDY IN TERMS OF EVALUATING THE
9 LINEARITY OF THE TOXICOKINETICS; IS THAT CORRECT?

10 A NO, I PLACED EQUAL WEIGHT ON BOTH STUDIES.
11 I SAID THAT THE ZEIGER STUDY WAS MORE POWERFUL BECAUSE
12 THEY USED MORE ANIMALS AND THEY ALSO COUNTED MORE CELLS
13 TO EVALUATE THE NUMBERS OF MICRONUCLEI.

14 Q LET'S TAKE A LOOK AT YOUR SLIDE NUMBER 36.
15 THIS IS YOUR TABLE SETTING FORTH THE DATA
16 FROM ZEIGER; IS THAT CORRECT?

17 A YES.

18 Q NOW --

19 A WITH THE EXCEPTION OF THE "DOSE PLUS DIET"
20 COLUMN, WHICH ZEIGER DID NOT INCLUDE.

21 Q WELL, THAT IS WHAT I WANTED TO FOCUS ON. AS
22 A THRESHOLD MATTER, THE TABLE THAT WE ARE LOOKING AT HERE
23 IN SLIDE NUMBER 36 IS NOT A REPLICA OF THE TABLE THAT WAS
24 SEEN IN THE ZEIGER PAPER; IS IT?

25 A IT IS NOT A REPLICA, IT IS BASED UPON ALL
26 THE SAME DATA. THE ONLY COLUMN OR THE ONLY NEW
27 INFORMATION THAT I ADDED WAS RELATED TO THE DIETARY
28 CONTRIBUTION.

1 Q SO YOU ADDED SOME INFORMATION IN THE CONTEXT
2 OF THE DOSE DIET, WHAT IS REFLECTED HERE AS THE SECOND
3 COLUMN FROM THE LEFT; CORRECT?

4 A YES.

5 Q THAT IS WHAT YOU ADDED, AND YOU ALSO OMITTED
6 CERTAIN INFORMATION FROM YOUR TABLE NUMBER 36 AS WELL;
7 CORRECT?

8 MR. METZGER: FROM YOUR TABLE?

9 THE WITNESS: I DON'T KNOW WHAT YOU ARE REFERRING
10 TO, SIR.

11 Q BY MR. SCHURZ: DIRECTING YOUR ATTENTION TO
12 THE FAR RIGHT-HAND SIDE COLUMN, WHERE IT READS THE NUMBER
13 AND THEN IT SAYS "M.N."?

14 A MICRONUCLEI.

15 Q "MICRONUCLEI PER 1,000 CELLS." DO YOU SEE
16 THAT?

17 A YES.

18 Q DOES THAT ACCURATELY RECORD ALL OF THE
19 INFORMATION THAT WAS INCLUDED IN THE ZEIGER PAPER?

20 A IT WAS BASED UPON PULLING OUT THE DATA
21 EXACTLY AS THEY WERE LISTED IN THE ZEIGER PAPER FOR ALL
22 ANIMALS PER DOSE GROUP, TOTAL NUMBER OF CELLS ANALYZED IN
23 THE FIRST -- FOR THE CONTROL GROUP, IT WAS 13,416,000.

24 Q BUT, IN FACT, IN THIS TABLE THAT WE ARE --
25 THAT YOU HAVE REPRODUCED HERE, YOU OMITTED CERTAIN
26 INFORMATION FROM THAT RIGHT-HAND COLUMN; DID YOU NOT?

27 A NOT THAT I AM AWARE OF.

28 Q WHY DON'T WE TAKE A LOOK AT THE ZEIGER

1 PAPER, AND SHOWING YOU WHAT IS EXHIBIT 2256.

2 A ALL RIGHT.

3 Q NOW, FIRST, JUST BY WAY OF ORIENTATION, WHAT
4 THE ZEIGER PAPER WAS DESIGNED TO EVALUATE HERE IS TO
5 EXAMINE THE ACRYLAMIDE DOSE-RESPONSE RELATIONSHIP AT LOW
6 DOSES AND TO INVESTIGATE WHETHER OR NOT THE INDUCTION OF
7 MICRONUCLEI WAS A THRESHOLD PHENOMENON; CORRECT?

8 A I THINK THAT IS WHAT THEY STATED, YES.

9 Q SO WHAT THE AUTHORS ARE PRINCIPALLY
10 INTERESTED IN IS EVALUATING WHETHER, AT LOW DOSES,
11 ACRYLAMIDE HAS A THRESHOLD RESPONSE OR WHETHER IT MAY BE
12 CHARACTERIZED AS A LINEAR RESPONSE; IS THAT CORRECT?

13 A I THINK THAT WAS ONE OF THEIR OBJECTIVES,
14 YES.

15 Q AND A THRESHOLD PHENOMENON, AS YOU HAVE
16 DISCUSSED IT, MEANS THAT THERE IS, IN FACT, NO DOSE-
17 RESPONSE BELOW A CERTAIN LEVEL; CORRECT?

18 A IN THIS CASE, THERE WOULD BE NO INCREASE IN
19 MICRONUCLEATED CELLS BELOW THE SO-CALLED THRESHOLD LEVEL.

20 Q NOW, LET'S GO BACK TO YOUR TABLE AND THE FAR
21 RIGHT-HAND COLUMN HERE.

22 AS YOU SIT HERE TODAY, DO YOU RECALL
23 OMITTING ANY INFORMATION THAT WAS INCLUDED BY THE ZEIGER
24 INVESTIGATORS IN THEIR COLLECTION OF THE DATA AS IT
25 RELATES TO THE MICRONUCLEI INDUCTION IN PERIPHERAL RED
26 BLOOD CELLS IN MICE?

27 A I ONLY FOCUSED ON THE SO-CALLED N.C.E. DATA
28 BECAUSE ZEIGER ET AL. FOUND THE OTHER -- THERE WERE TWO

1 END POINTS THAT WERE MEASURED. ONE WERE THE
2 RETICULOCYTES AND THE OTHER WERE WHAT THEY CALLED N.C.E.,
3 SO WHAT DOES THAT STAND FOR, NORMOCHROMATIC ERYTHROCYTE.

4 Q NORMOCHROMATIC ERYTHROCYTE JUST MEANS NORMAL
5 CONCENTRATION OF HEMOGLOBIN; RIGHT?

6 A I AM NOT SURE THAT -- IT WOULD MEAN
7 SOMETHING RELATED TO THE -- I WOULD ASSUME THE CHROMATIN
8 THAT IS PRESENT IN THE MICRONUCLEI.

9 Q WHAT WE ARE TALKING ABOUT HERE IS RED BLOOD
10 CELLS; RIGHT?

11 A RED BLOOD CELLS.

12 Q SO, AGAIN, FOCUSING ON YOUR TABLE AND THE
13 INFORMATION THAT IS CAPTURED IN THE FAR RIGHT-HAND
14 COLUMN, LET'S TAKE A LOOK AT TABLE NUMBER 2 IN
15 EXHIBIT 2256, WHICH CAN BE FOUND AT PAGE 250 OR 2256-004.

16 A ALL RIGHT.

17 Q LET ME KNOW WHEN YOU HAVE THAT IN FRONT OF
18 YOU.

19 A I HAVE IT.

20 Q DIRECTING YOUR ATTENTION TO THE SECOND
21 COLUMN FROM THE RIGHT, HERE WE HAVE THE COLUMN THAT IS
22 DENOMINATED THE MICRONUCLEI OR THE N.C.E., THE
23 NORMOCHROMATIC ERYTHROCYTES.

24 DO YOU SEE THAT?

25 A YES.

26 Q IN EACH CASE, THE INVESTIGATORS INCLUDED A
27 STANDARD DEVIATION FOR ALL OF THE VALUES THAT THEY
28 INCLUDED; CORRECT?

1 A YES, THEY DID.

2 Q AND THAT WAS A PIECE OF INFORMATION YOU
3 CHOSE NOT TO INCLUDE IN YOUR TABLE; CORRECT?

4 A WELL, THEY HAD ACCESS TO THE DATA FROM THE
5 INDIVIDUAL ANIMALS. I DID NOT HAVE THAT. I USED ALL OF
6 THE ANIMALS IN EACH DOSE GROUP FOR MY CALCULATIONS. SO I
7 USED THE TOTAL NUMBER OF CELLS, N.C.E. CELLS THAT WERE
8 SCORED. SO WHEN YOU SEE 13,416,986 FOR THE FIRST ROW,
9 THAT IS EXACTLY THE NUMBER THAT I USED.

10 Q LET'S JUST FOCUS ON WHAT THE INVESTIGATORS
11 REPORTED, IF YOU WOULD, WITH RESPECT TO THE ZEIGER TABLE
12 NUMBER 2.

13 A SEE, I COULD NOT CALCULATE THE STANDARD
14 DEVIATION.

15 Q NO, BUT THE INVESTIGATORS INCLUDED A
16 STANDARD DEVIATION; CORRECT?

17 A YES, AND THIS IS ACROSS ANIMALS.

18 Q YES. NOW, WITH RESPECT TO THAT STANDARD
19 DEVIATION, THEY INCLUDED THE STANDARD DEVIATION AS A WAY
20 OF MEASURING THE POTENTIAL VARIATION; CORRECT?

21 A ACROSS ANIMALS. IT IS THE VARIATION ACROSS
22 ANIMALS.

23 Q THEN WHAT THEY DID IS TO INDICATE FURTHER A
24 P-VALUE WHERE THEY SHOWED A SIGNIFICANT INCREASE VERSUS
25 CONTROLS.

26 DO YOU SEE THAT?

27 IT IS A NOTE AT THE BOTTOM OF THE TABLE AND
28 IT INDICATES A P-VALUE VERSUS CONTROLS; CORRECT?

1 A THAT IS CORRECT.

2 Q WHAT THE INVESTIGATORS SHOW AND CONCLUDED
3 WAS THAT THE P-VALUE DID NOT REFLECT A SIGNIFICANT
4 INCREASE OVER CONTROLS UNTIL YOU REACH A DOSE LEVEL OF
5 4.0; CORRECT?

6 A YES.

7 Q THAT IS THE FIRST PLACE WE SEE ASTERISKS IN
8 THE ZEIGER PAPER; CORRECT?

9 A YES, BUT THIS IS -- THESE COMPARISONS, THESE
10 PAIRWISE COMPARISONS ARE VERY LOW POWER. YOU ONLY HAVE
11 TEN ANIMALS PER DOSE GROUP. SO YOU HAVE A RELATIVELY
12 LARGE STANDARD DEVIATION IN EACH CASE. SO WHEN YOU -- AS
13 I SAID THIS MORNING, ONE OF THE STATISTICAL PROBLEMS THAT
14 YOU HAVE TO OVERCOME IN A STUDY LIKE THIS IS COMPARING
15 TWO MEAN VALUES WHEN YOU HAVE A VERY LARGE BACKGROUND,
16 AND YOU HAVE GOT VALUES THAT ARE CLOSE TO THE BACKGROUND.
17 WITH ONLY TEN ANIMALS, THE POWER TO MAKE THAT DISTINCTION
18 BECOMES EXTREMELY SMALL. THAT IS WHY I SAID THIS
19 MORNING, YOU HAVE TO LOOK AT THE TOTALITY OF THE DATA,
20 INVESTIGATE THE LINEARITY OF THE MODELS, AS I SUGGESTED
21 THIS MORNING, AND ON THE BASIS OF THAT ANALYSIS,
22 DETERMINE WHETHER THERE IS ANY SIGNIFICANT DEVIATION FROM
23 LINEARITY. THAT IS WHAT I DID.

24 I SHOULD ALSO SAY THAT FENNEL DID THAT AS
25 WELL. THEY ALSO AGREED THAT THE LINEAR MODEL PROVIDED AN
26 EXCELLENT FIT TO THESE DATA.

27 Q SO LET'S FOCUS ON THE INVESTIGATORS'
28 CONCLUSIONS, IF I MAY, WITH RESPECT TO THE ZEIGER STUDY.

1 A OKAY.

2 Q NOW, IN THE VARIOUS DOSES THAT THEY MEASURED
3 HERE, THE CONTROL IS MEASURED AT ZERO; CORRECT?

4 THAT RECORDS MICRONUCLEI AND THE RED BLOOD
5 CELLS OF 1.40 WITH THE STANDARD DEVIATION OF 0.07;
6 CORRECT?

7 A YES.

8 Q AND YOU HAVE TO GET TO 4.0 UNTIL YOU SEE A
9 CONCLUSION BY THE AUTHORS THAT THERE IS A SIGNIFICANT
10 INCREASE IN TERMS OF DOSE, CORRECT, WHICH IS WHY THEY
11 INCLUDE FOR THE FIRST VALUE AT 4.0 THE ASTERISK SHOWING
12 THE PROBABILITY VALUE OF LESS THAN 0.05?

13 A YES, BUT AS I JUST INDICATED, THE ABILITY TO
14 DETECT A SIGNIFICANT DIFFERENCE IN THE MEAN VALUE AT
15 THESE LOW LEVELS IS EXTREMELY SMALL. YOU WOULD REQUIRE
16 EXPERIMENTS WITH MUCH LARGER NUMBERS OF ANIMALS TO
17 PROVIDE SUFFICIENT POWER TO FIND THE SMALL DIFFERENCE.

18 Q SO UNDERSTANDING THAT, WHAT THE AUTHORS
19 CONCLUDED IN THIS CASE IS THAT THE INCREASE OF DOSE IN
20 THIS CASE DID NOT RESULT IN A STATISTICALLY SIGNIFICANT
21 INCREASE FROM BACKGROUND LEVELS OF THE MICRONUCLEI UNTIL
22 YOU HIT A LEVEL OF 4.0?

23 A I THINK I HAVE ANSWERED THIS QUESTION TWICE
24 NOW.

25 Q NOW, WHAT THE AUTHORS CONCLUDE FROM THESE
26 DATA SETS IS THAT THE DATA DEMONSTRATES THAT THE
27 INDUCTION BY ACRYLAMIDE OF CHROMOSOME DAMAGE IN THE BONE
28 MARROW EXHIBITS AN APPARENT THRESHOLD; CORRECT?

1 A THEY SAID THAT IN A NUMBER OF PLACES, BUT
2 THE ABILITY TO DETECT A THRESHOLD BY THIS PARTICULAR
3 ANALYSIS IS REMARKABLY SMALL.

4 Q SO YOU DISAGREE WITH THE AUTHOR'S
5 CONCLUSIONS WITH RESPECT TO ONE OF THE TWO PAPERS THAT
6 YOU HAVE CITED?

7 A INSOFAR AS THEY OFFERED SOME SUGGESTION THAT
8 THERE WAS A THRESHOLD, YES.

9 Q SO LET'S TAKE A LOOK AT THEIR CONCLUSION AT
10 PAGE 256, AND WE WERE LOOKING AT THIS A LITTLE BIT
11 EARLIER.

12 AGAIN, FOCUSING ON 256, THE LEFT-HAND COLUMN
13 OF THE ZEIGER PAPER THAT YOU RELY ON, WE WERE LOOKING
14 EARLIER AT THE FIRST SENTENCE THAT INDICATED THE STUDY
15 WAS DESIGNED PRIMARILY TO EXAMINE THE ACRYLAMIDE DOSE-
16 RESPONSE RELATIONSHIP; CORRECT?

17 DO YOU SEE WHERE I AM?

18 A ON PAGE 25 --

19 Q IT IS 256 OR 256-010. IT IS THE PARAGRAPH
20 THAT BEGINS, "THE STUDY WAS DESIGNED PRIMARILY TO
21 EXAMINE" --

22 A YES.

23 Q OKAY. SO THE AUTHORS INDICATE THAT THE
24 PURPOSE OF THE STUDY WAS TO EXAMINE THE ACRYLAMIDE
25 DOSE-RESPONSE RELATIONSHIP AT LOW DOSES AND TO
26 INVESTIGATE WHETHER OR NOT THE INDUCTION OF MICRONUCLEI
27 WAS A THRESHOLD PHENOMENON.

28 AND THE AUTHORS CONCLUDE, DR. RAPPAPORT,

1 THAT THE STUDY, QUOTE, "IT APPEARED TO HAVE ACCOMPLISHED
2 THAT GOAL AND THE DATA SUPPORTS THE EXISTENCE OF A
3 THRESHOLD FOR THE MICRONUCLEI IN RED BLOOD CELLS AT ONE
4 OR TWO MILLIGRAMS PER KILOGRAMS PER DAY."

5 CORRECT?

6 A THEY SAY THAT, BUT THEY ARE QUITE WRONG.

7 Q OKAY. ALL RIGHT. AND THEY FURTHER SAY, DO
8 THEY NOT, AT THE LAST SENTENCE OF THE ARTICLE, THEY SAY,
9 "IN ADDITION, THE DATA DEMONSTRATES THAT THE INDUCTION BY
10 ACRYLAMIDE OF CHROMOSOME DAMAGE IN THE BONE MARROW
11 EXHIBITS AN APPARENT THRESHOLD."

12 CORRECT?

13 A YES, THEY SAY THAT, BUT I DISAGREE
14 COMPLETELY.

15 Q NOW, THE ZEIGER PAPER EVALUATED THREE
16 DIFFERENT DOSE METRICS; CORRECT?

17 A ARE YOU TALKING ABOUT THE DIFFERENT
18 MICRONUCLEI END POINTS?

19 Q I AM TALKING ABOUT --

20 A YOU ARE TALKING ABOUT THE ADDUCTS AS WELL?

21 Q YES, I AM.

22 A THEY LOOKED AT MICRONUCLEI, THEY LOOKED AT
23 D.N.A. ADDUCTS, AND THEY LOOKED AT HEMOGLOBIN ADDUCTS.

24 Q WITH RESPECT TO THE HEMOGLOBIN ADDUCTS OR
25 THE D.N.A. ADDUCTS, WHEN THOSE WERE USED AS THE DOSE
26 METRICS, THE INVESTIGATORS IN ZEIGER CONCLUDED THAT THERE
27 WAS, QUOTE, "THE RESPONSE WAS SIGNIFICANTLY NON-LINEAR
28 AND MODELS THAT ASSUMED A THRESHOLD DOSE OF ONE TO TWO

1 MILLIGRAMS PER KILOGRAMS PER DAY PROVIDED A BETTER FIT
2 THAN A LINEAR MODEL."

3 CORRECT?

4 A YES, THEY SAID THAT, BUT AGAIN, I COMPLETELY
5 DISAGREE.

6 Q NOW, IF WE COULD TAKE A LOOK AT THE ABSTRACT
7 AT 02256-001, AND DIRECTING YOUR ATTENTION TO THE
8 LANGUAGE MIDWAY THROUGH WHERE IT BEGINS, "HOWEVER," LET'S
9 SEE. YES.

10 "WHEN HEMOGLOBIN OR D.N.A. ADDUCTS WERE USED
11 AS A DOSE METRIC, THE RESPONSE WAS SIGNIFICANTLY
12 NON-LINEAR."

13 CORRECT?

14 A YES, THEY SAY THAT, BUT THEY DID NOT GO
15 THROUGH A RIGOROUS GOODNESS OF FIT EXERCISE AS I DID. SO
16 THEIR CONCLUSION HAS TO BE TEMPERED WITH THE METHODS THAT
17 THEY USED, WHICH WERE POORLY DESCRIBED IN THE PAPER
18 INsofar AS THEY ARE TRYING TO LOOK FOR NON-LINEAR
19 EFFECTS.

20 Q ULTIMATELY, IF WE COULD SEE THE BOTTOM OF
21 THE ABSTRACT IN WHICH THE ZEIGER AUTHORS OFFER THEIR
22 CONCLUSION, THEY FINALLY STATE THAT THESE DATA SUGGEST A
23 THRESHOLD FOR ACRYLAMIDE IN THE MICRONUCLEI TEST;
24 CORRECT?

25 A YES, THEY SAY THAT, BUT I THINK THE EVIDENCE
26 SUPPORTING THAT PARTICULAR CONCLUSION IS VERY WEAK.

27 Q SO YOU HAVE USED THIS STUDY AS A WAY OF
28 SUPPORTING YOUR HYPOTHESIS OR YOUR OPINION THAT THE

1 LINEAR MODEL PROVIDES THE BEST FIT, BUT THE ACTUAL
2 INVESTIGATORS CONCLUDED THAT THE DATA SUGGESTS A
3 THRESHOLD FOR ACRYLAMIDE IN THE MICRONUCLEI TEST;
4 CORRECT?

5 A THEY SAY THAT. IF THEY HAD GONE THROUGH THE
6 SAME EXERCISE THAT I DID, THEY WOULD NOT HAVE MADE THAT
7 CONCLUSION. THEY DID -- IT IS IMPORTANT TO SAY THAT WHEN
8 THEY USED ADMINISTRATIVE -- ADMINISTERED DOSE OF
9 ACRYLAMIDE AS THE INDEPENDENT VARIABLE, THE X AXIS, THEY
10 HAVE A VERY STRONG LINEAR RELATIONSHIP, THE SAME AS I
11 DID, AND THEY SAID THERE IS NO EVIDENCE OF NON-LINEARITY
12 WHEN USING ADMINISTERED DOSE VERSUS MICRONUCLEI.

13 SO IN THAT SENSE, THEIR DATA OR THEIR
14 CONCLUSIONS AND MINE WERE CONSISTENT.

15 Q ALL RIGHT. NOW, AGAIN, WITH RESPECT TO THE
16 ZEIGER TABLE THAT WE HAVE BEEN LOOKING AT AS TABLE
17 NUMBER 2, YOU CHOSE NOT TO INCLUDE A PROBABILITY VALUE OR
18 A STANDARD DEVIATION; CORRECT?

19 A OKAY. THERE IS NO WAY THAT I COULD COMPUTE
20 A STANDARD DEVIATION FROM THE DATA THAT WERE AVAILABLE.
21 THEY DID NOT PROVIDE THE DATA FOR THE INDIVIDUAL ANIMALS.
22 SO I COULD NOT HAVE DONE THAT FROM THAT TEST.

23 Q SO LOOKING AT THE DATA SET THAT ZEIGER WAS
24 ANALYZING AND UPON WHICH THEY MADE A DETERMINATION THAT
25 THE DATA REFLECTS A THRESHOLD AS OPPOSED TO A LINEAR
26 RESPONSE, WHAT THE INVESTIGATORS IN ZEIGER CONCLUDED IS
27 THAT ALL OF THE INCREASE IN DOSE FROM ZERO ALL THE WAY UP
28 TO FOUR, NONE OF IT MADE, IN EFFECT, ANY DIFFERENCE IN

1 TERMS OF STATISTICAL SIGNIFICANCE FROM THE BASE; CORRECT?

2 A NO, NOT CORRECT. THIS IS A VERY LOW POWER
3 DETERMINATION. THEY ARE COMPARING THE MEAN VALUE FROM
4 TEN ANIMALS WITH A VERY HIGH BACKGROUND LEVEL. IT WOULD
5 BE EXTREMELY DIFFICULT TO FIND A SIGNIFICANT DIFFERENCE
6 IN THE SMALL CHANGES IN MICRONUCLEI AT THE LOW-DOSE LEVEL
7 WITH SUCH A LARGE BACKGROUND.

8 IF YOU COULD SHOW MY SLIDE WHICH SHOWS THE
9 LINEAR RELATIONSHIP THAT I DON'T THINK WE REALLY LOOKED
10 AT THIS MORNING, I THINK YOU WOULD SEE VERY CLEARLY WHAT
11 IS GOING ON HERE.

12 Q WHAT THE AUTHORS CONCLUDED IN ZEIGER,
13 HOWEVER, BASED UPON THE VALUES THAT THEY REPORTED IN
14 TABLE 2, INCLUDING THE STANDARD DEVIATION, THAT THE DATA
15 WERE CONSISTENT WITH A THRESHOLD FOR ACRYLAMIDE IN THE
16 MICRONUCLEI TESTS; CORRECT?

17 A COUNSELOR, THEY ARE TAKING A LARGE STUDY AND
18 THEY ARE BREAKING IT DOWN INTO LITTLE TINY PIECES, AND
19 THEY ARE USING THOSE LITTLE PIECES TO TRY TO MAKE SOME
20 KIND OF ARGUMENT IN FAVOR OF A THRESHOLD. I WAS ARGUING
21 THIS MORNING THAT THAT IS NOT A GOOD IDEA. THAT YOU NEED
22 TO USE THE TOTALITY OF THE DATA FROM ALL THE ANIMALS,
23 LOOKING AT THE LINEARITY OF THE RESPONSE.

24 IF WE COULD SHOW -- IF WE COULD SHOW A SLIDE
25 WITH MY RELATIONSHIP THAT I ESTIMATED, I THINK YOU WOULD
26 SEE WHAT IS GOING ON.

27 Q DR. RAPPAPORT, I AM SURE MR. METZGER WILL
28 GIVE YOU THE OPPORTUNITY --

1 THE COURT: JUST ASK THE NEXT QUESTION.

2 Q BY MR. SCHURZ: SO YOU IDENTIFIED TWO
3 STUDIES IN SUPPORT OF YOUR PROPOSITION THAT THE LINEAR
4 MODEL WAS CONSISTENT WITH WHAT YOU SEE AS THE
5 TOXICOKINETICS OF ACRYLAMIDE; CORRECT?

6 A YOU MEAN THE ABRAMSSON-ZETTERBERG, AND YES,
7 I USED THE DATA FROM THOSE TWO STUDIES.

8 Q WITH RESPECT TO THE ZEIGER STUDY THAT WE
9 HAVE BEEN DISCUSSING, THE AUTHORS WOULD RESPECTFULLY
10 DISAGREE WITH THE PROPOSITION AND SUGGEST THAT IT IS
11 ACTUALLY A THRESHOLD THAT IS AT WORK HERE, AND THAT THE
12 -- WHETHER EVALUATING WHETHER THE D.N.A. ADDUCTS OR THE
13 HEMOGLOBIN ADDUCTS, THAT THE EFFECT IS NOMINAL; CORRECT?

14 A WITH REGARDS TO THE HEMOGLOBIN AND D.N.A.
15 ADDUCTS, THERE ARE OTHER ISSUES THAT ARE INVOLVED HERE.

16 Q ALL RIGHT.

17 MR. METZGER: WERE YOU FINISHED WITH YOUR ANSWER?

18 THE WITNESS: THE MICRONUCLEI ARE MEASURES OF
19 GENETIC DAMAGE IN THE BONE MARROW. THE HEMOGLOBIN IS
20 MEASURED IN THE BLOOD. THE D.N.A. ADDUCTS WERE MEASURED
21 IN THE LIVER. THEY MAY NOT REFLECT THE TOXICOKINETIC
22 PROCESSES THAT WERE AT WORK IN THE BONE MARROW. THE
23 MICRONUCLEI VERSUS ADMINISTERED DOSE, WHICH TAKES INTO
24 ACCOUNT ALL TOXICOKINETICS THAT ARE INVOLVED IN THE
25 PRODUCTION OF MICRONUCLEI, WOULD INCLUDE ANY SUCH
26 PROCESSES.

27 Q BY MR. SCHURZ: ARE YOU FINISHED?

28 A I AM.

1 Q I APOLOGIZE IF I HAVE BEEN CUTTING YOU OFF.
2 LET'S TALK ABOUT THE ABRAMSSON ARTICLE,
3 WHICH YOU HAVE ALSO CITED AT SLIDE NUMBER 35 FOR THE
4 PROPOSITION THAT THE LINEAR MODEL IS APPROPRIATE.

5 HERE, AGAIN, YOU INCLUDE DATA FROM THE
6 ABRAMSSON-ZETTERBERG STUDY; IS THAT CORRECT?

7 A YES.

8 Q ONCE AGAIN, YOU HAVE ELECTED TO DO SOME
9 EDITING OF THE INFORMATION THAT APPEARS IN THE ORIGINAL
10 TABLE; CORRECT?

11 A NO, SIR, I DID NOT ELECT TO DO ANY EDITING
12 AT ALL. I USED THE DATA THAT THEY PROVIDED.

13 Q DID YOU INCLUDE THE STANDARD DEVIATION THAT
14 THE INVESTIGATORS INCLUDED?

15 A I WAS NOT ABLE TO ESTIMATE THE STANDARD
16 DEVIATION FOR THE SAME REASON THAT I COULD NOT ESTIMATE
17 THE STANDARD DEVIATION FROM THE ZEIGER STUDY.

18 Q YOU DID NOT CALCULATE A STANDARD DEVIATION;
19 CORRECT?

20 A THEY PRESENTED ONE BECAUSE THEY HAD ACCESS
21 TO THE ORIGINAL ANIMALS.

22 Q AND YOU DID NOT DO A PROBABILITY TESTING FOR
23 PURPOSES OF DETERMINING WHETHER THERE WAS A SIGNIFICANT
24 INCREASE FROM DIFFERENT DOSE GROUPS IN THE ABRAMSSON-
25 ZETTERBERG DATA; CORRECT?

26 A NO, I COULD NOT, AND IN FACT, I WOULD NOT
27 BECAUSE I DON'T THINK THAT WOULD BE AN APPROPRIATE TEST
28 BECAUSE IT WOULD BE ANOTHER LOW POWER DETERMINATION

1 COMPARING TWO MEANS FROM POPULATIONS WITH A LARGE
2 BACKGROUND.

3 Q SO LET'S TAKE A LOOK AT THE ABRAMSSON-
4 ZETTERBERG PAPER, WHICH HAS BEEN IDENTIFIED AS
5 PLAINTIFF'S EXHIBIT 484.

6 A YES, I HAVE IT.

7 Q ALL RIGHT. IS THIS THE ABRAMSSON PAPER ON
8 WHICH YOU ARE RELYING?

9 A YES.

10 Q SO LET ME ASK YOU TO TAKE A LOOK AT TABLE
11 NUMBER 1, WHICH IS AT 484-006.

12 LET ME KNOW WHEN YOU HAVE GOT THAT IN FRONT
13 OF YOU.

14 A I HAVE IT.

15 Q LET ME DIRECT YOUR ATTENTION TO THE BOTTOM
16 PORTION OF THIS TABLE IN EXHIBIT 484-006. HERE WE SEE
17 SOME OF THE VALUES THAT YOU HAVE CAPTURED IN YOUR SLIDE
18 NUMBER 35 WITH RESPECT TO THE MEAN THAT IS INCLUDED IN
19 THE FAR RIGHT-HAND COLUMN; CORRECT?

20 A YES, I ASSUME THAT THEY ARE THE SAME MEANS,
21 CORRECT.

22 Q AND AGAIN, IF WE CAN JUST LOOK AT THE FIRST
23 LINE, THIS IS OUR CONTROL GROUP; CORRECT?

24 A YES.

25 Q THIS -- WHEN WE SEE A ZERO, THAT TELLS US
26 THE BACKGROUND LEVEL THAT THE INVESTIGATOR IN ABRAMSSON-
27 ZETTERBERG FOUND WITH RESPECT TO THE MALE MICE; CORRECT?

28 A IN REGARD TO THE NUMBER OF MICRONUCLEATED

1 CELLS, CORRECT.

2 Q WHAT -- AGAIN, WHAT THE AUTHOR PERFORMED IN
3 THIS CASE WAS TO INDICATE AT WHAT POINT IS THERE A
4 STATISTICALLY SIGNIFICANT INCREASE AS A RESULT OF AN
5 INCREASE IN DOSE BY AFFIXING AN ASTERISK WHERE, AS YOU
6 CAN SEE IN THE NOTES, IT INDICATES THE ASTERISK MEANS
7 "SIGNIFICANT DIFFERENCE FROM THE CONTROL GROUP."

8 DO YOU SEE THAT?

9 A YES.

10 Q WHAT THE INVESTIGATORS IN ABRAMSSON-
11 ZETTERBERG CONCLUDED WAS THAT THERE WAS NO SIGNIFICANT
12 DIFFERENCE FROM THE CONTROL GROUP UNTIL YOU REACHED A
13 DOSAGE OF SIX MILLIGRAMS PER KILOGRAM OF BODY WEIGHT;
14 CORRECT?

15 A YES, BUT AGAIN, IT GOES BACK TO THE POINT
16 THAT THEY WEREN'T REALLY ABLE TO DETECT A SMALL
17 DIFFERENCE IN THESE GROUPS BECAUSE THEY ONLY HAD FIVE
18 ANIMALS PER GROUP. THEY ALSO CONCLUDED, AS DID ZEIGER,
19 THAT OVER THE FULL RANGE OF EXPOSURES, THEY SAW A REALLY
20 GOOD FIT TO A LINEAR MODEL, WHICH IS EXACTLY WHAT I
21 FOUND.

22 Q BUT THE ABSENCE OF A STATISTICALLY
23 SIGNIFICANT DOSE-RESPONSE IN THIS LOW RANGE, NAMELY AT
24 THE DOSES OF ONE AND THREE, IS CONSISTENT, IS IT NOT,
25 WITH THE CONCLUSION IN ZEIGER THAT THERE IS A THRESHOLD?

26 A NO, IT IS NOT. THEY LOOKED AT THE LINEARITY
27 OF THE RELATIONSHIP AND THEY FOUND A VERY STRONG LINEAR
28 TREND. THIS PAIRWISE COMPARISON, I THINK I HAVE SAID IT

1 TEN TIMES, AND I AM NOT GOING TO CHANGE MY OPINION, HAS
2 VERY LOW POWER TO DETECT A DIFFERENCE. IT IS A FOREGONE
3 CONCLUSION THAT YOU ARE NOT GOING TO BE ABLE TO DETECT A
4 DIFFERENCE UNTIL THE DOSE LEVEL GETS VERY HIGH AND THE
5 MICRONUCLEI LEVEL IS LARGE ENOUGH TO OVERCOME THIS
6 UNCERTAINTY YOU HAVE BECAUSE OF THE VARIATION ACROSS
7 ANIMALS.

8 Q IT IS EXACTLY THAT EFFECT, IS IT NOT,
9 DR. RAPPAPORT, THAT THE INVESTIGATORS IN ZEIGER FOUND
10 THAT BECAUSE THERE WAS NO DOSE-RESPONSE AT THESE LOW
11 LEVELS, THAT THE LINEAR MODEL DID NOT PROVIDE A GOOD FIT,
12 AND THAT MODELS ASSUMING A THRESHOLD DOSE PROVIDED A
13 BETTER FIT?

14 A NO, THEY DID NOT CONCLUDE THAT AT ALL. WITH
15 REGARD TO THE USE OF ADMINISTERED DOSE AS THE INDEPENDENT
16 VARIABLE, THEY FOUND A VERY STRONG LINEAR RELATIONSHIP
17 BETWEEN DOSE AND MICRONUCLEI AND NO EVIDENCE OF A
18 NON-LINEAR TREND.

19 Q I'M SORRY, I WAS SPEAKING OF ZEIGER.

20 A YES, THAT IS WHAT ZEIGER CONCLUDED.

21 Q ALL RIGHT. SO LET'S GO BACK THEN.

22 THE COURT: MR. SCHURZ, HOW MUCH LONGER ARE YOU
23 GOING TO BE WITH THIS WITNESS?

24 MR. SCHURZ: LESS THAN FIVE MINUTES, YOUR HONOR. I
25 AM WRAPPING UP.

26 THE COURT: GO AHEAD.

27 Q BY MR. SCHURZ: IF WE CAN GO BACK TO THE
28 ZEIGER ARTICLE AT 2256. IF I COULD DIRECT YOUR ATTENTION

1 TO THE AUTHORS' CONCLUSION.

2 HERE, DR. RAPPAPORT, WHERE THEY STATE,
3 "HOWEVER, WHEN HEMOGLOBIN OR D.N.A. ADDUCTS WERE USED AS
4 THE DOSE METRIC, THE RESPONSE WAS SIGNIFICANTLY
5 NON-LINEAR."

6 A YES --

7 Q "AND MODELS THAT ASSUMED A THRESHOLD DOSE OF
8 ONE OR TWO MILLIGRAMS PER KILOGRAMS PER DAY PROVIDED A
9 BETTER FIT THAN A LINEAR MODEL."

10 THAT WAS THE CONCLUSION OF THE ZEIGER
11 INVESTIGATORS; CORRECT?

12 A YES, AS I SAID BEFORE, THIS WASN'T THE
13 RELATIONSHIP I WAS INVESTIGATING. I TRIED TO SUGGEST
14 THAT SINCE MICRONUCLEI ARE FORMED IN THE BONE MARROW, WE
15 REALLY NEED TO LOOK AT THE ADMINISTERED DOSE AND COMPARE
16 THE KINETIC PROCESSES WITH ADMINISTERED DOSE AND NOT WITH
17 THE USE OF EITHER HEMOGLOBIN OR D.N.A. ADDUCTS, WHICH
18 COME FROM THE BLOOD OR FROM THE LIVER, AS THE EXPOSURE
19 METRIC.

20 THE AUTHORS CONCLUDED WITH REGARD TO USE OF
21 ADMINISTERED DOSE THAT THE LINEAR MODEL WAS FULLY
22 APPROPRIATE. SO WE AGREED ON THAT.

23 Q WITH RESPECT TO ONE OF THE THREE DOSE
24 METRICS THEY EVALUATED, THEY BELIEVED THAT THE LINEAR
25 MODEL WAS APPROPRIATE; CORRECT?

26 A YES, THE ADMINISTERED DOSE, WHICH IS THE
27 MOST RELEVANT ONE IN OUR CONTEXT.

28 Q NOW, THERE WAS SOME DISCUSSION EARLIER TODAY

1 WITH RESPECT TO YOUR PUBLICATIONS REGARDING ADDUCTS AND
2 WE SAW A SERIES OF SLIDES WITH RESPECT TO THOSE
3 PUBLICATIONS. NONE OF THOSE PUBLICATIONS INVOLVE ADDUCTS
4 INVOLVING ACRYLAMIDE; IS THAT CORRECT?

5 A CORRECT.

6 MR. SCHURZ: THANK YOU, YOUR HONOR. NOTHING
7 FURTHER.

8 THE COURT: ALL RIGHT.

9 MR. METZGER: IT IS GOING TO BE BRIEF REDIRECT.

10 THE COURT: HOW LONG?

11 MR. METZGER: I THINK FIVE MINUTES.

12 THE COURT: ALL RIGHT. FIVE MINUTES.

13

14 REDIRECT EXAMINATION

15

16 BY MR. METZGER:

17 Q COULD WE BRING UP THE POWERPOINT.

18 WHILE WE ARE DOING THAT, LET ME ASK YOU ONE
19 THING, DR. RAPPAPORT. MR. SCHURZ ASKED YOU A QUESTION:
20 IS IT TRUE THAT D.N.A. ADDUCTS WERE NOT REPORTED IN THE
21 VIKSTROM STUDY?

22 DO YOU RECALL THAT DISCUSSION?

23 A YES.

24 Q DID THE VIKSTROM STUDY STUDY D.N.A. ADDUCTS?

25 A NO, IT WAS BASED ON HEMOGLOBIN ADDUCTS.

26 Q SO IN A STUDY OF HEMOGLOBIN ADDUCTS, THE
27 FACT THAT THEY DON'T REPORT D.N.A. ADDUCTS IS OF NO
28 SIGNIFICANCE BECAUSE THEY DID NOT LOOK FOR THEM; RIGHT?

1 A YES.

2 Q I JUST WANTED TO GET THAT CLEAR.
3 NOW, WE WILL GET TO THAT IN ONE SECOND.

4 THE ABRAMSSON-ZETTERBERG PAPER THAT COUNSEL
5 WAS DISCUSSING WITH YOU, EXHIBIT 484, WHAT IS THE TITLE
6 OF THAT PAPER?

7 A "THE DOSE-RESPONSE RELATIONSHIP AT VERY LOW
8 DOSES OF ACRYLAMIDE IS LINEAR IN THE FLOW CYTOMETER-BASED
9 MOUSE MICRONUCLEUS ASSAY."

10 Q THAT TITLE ACTUALLY STATES THEIR CONCLUSION;
11 DOES IT NOT?

12 A YES, THE AUTHORS CONCLUDED THAT IT WAS A
13 LINEAR RELATIONSHIP.

14 Q IN THE ABSTRACT, WHAT THEY WROTE WAS THE
15 DOSE-RESPONSE FUNCTION WAS FOUND TO BE LINEAR WITH A
16 TENDENCY TO HAVE A STEEPER RISE AT THE LOWEST DOSES?

17 A YES, THEY SAID THAT.

18 Q WHAT DOES THAT MEAN?

19 A IT MEANS THAT THE SLOPE OF THE RELATIONSHIP
20 IN THEIR INTERPRETATION WAS GREATER AT THE LOW-DOSE
21 LEVELS. I DID NOT FIND EVIDENCE OF THAT IN MY ANALYSIS.

22 Q WELL, NOW LET'S TAKE A LOOK AT YOUR
23 ANALYSIS. IN PARTICULAR, I WANT TO FOCUS ON YOUR
24 ANALYSIS OF WHETHER THE DATA EXHIBITED A THRESHOLD.

25 DO YOU HAVE THE POWERPOINT THERE?

26 COULD YOU DIRECT US TO WHICH PAGE THAT WE
27 SHOULD LOOK AT?

28 A PAGE 39. THIS IS THE RELATIONSHIP.

1 Q THIS IS IT. THE FIGURE YOU HAVE HERE IS
2 TITLED, "DOSE-RESPONSE RELATIONSHIP FROM SIMPLE LINEAR
3 REGRESSION, MODEL 1 OF MICRONUCLEATED ERYTHROCYTES ON THE
4 ADMINISTERED ACRYLAMIDE DOSE. DATA FROM ZEIGER AS SHOWN
5 IN TABLE 2."

6 EXPLAIN TO US WHY, IN YOUR OPINION, BASED
7 UPON YOUR GOODNESS OF FIT STATISTICAL ANALYSES, YOU
8 CONCLUDE THAT THE DATA FROM THESE STUDIES FROM ZEIGER
9 DOES NOT DEMONSTRATE A THRESHOLD?

10 A RIGHT. FIRST, I DID A RIGOROUS GOODNESS OF
11 FIT TEST BASED UPON THE STATISTICS THAT I PRESENTED THIS
12 MORNING, BUT BEYOND THAT, AND YOU CAN SAY THIS IS NOT
13 ROCKET SCIENCE, THERE IS A STRAIGHT LINE THAT IS DRAWN
14 HERE. IT IS VERY CLEAR THAT YOU SEE RANDOM VARIATION
15 ABOVE AND BELOW THE LINE OVER THE FULL RANGE, GOING DOWN
16 TO ZERO. IT IS A STRAIGHT LINE. IF YOU TAKE ANY TWO
17 POINTS DOWN IN THAT VERY LOW REGION, IT IS GOING TO BE
18 DIFFICULT TO SAY YES, THESE ARE STATISTICALLY DIFFERENT.
19 THAT IS WHAT ZEIGER ET AL. WERE BASING THEIR THRESHOLD
20 ARGUMENT ON, BUT YOU CAN SEE FROM THE FULLNESS OF THE
21 DATA, THERE IS NO EVIDENCE OF A THRESHOLD.

22 Q YOU SAY WE COULD SEE THAT FROM LOOKING AT
23 THIS GRAPH HERE, FIGURE 2, DID YOU ACTUALLY STATISTICALLY
24 SHOW THAT IN YOUR GOODNESS OF FIT STATISTICAL TESTING
25 ANALYSIS?

26 A YES. ABSOLUTELY. THERE WAS NO EVIDENCE OF
27 CURVATURE AND THERE WAS NO EVIDENCE OF A THRESHOLD.

28 Q COULD YOU SHOW US WHERE THAT IS?

1 A THAT WAS THE TABLE THAT PRECEDED.

2 Q ALL RIGHT. WHERE HERE DOES IT SHOW -- NO,
3 IT WAS THAT ONE YOU HAD THERE -- WHERE DOES IT SHOW THAT?

4 A THE ZEIGER STUDY IS THIS STUDY SHOWN AT THE
5 BOTTOM.

6 Q LET ME GET THE POINTER SO WE CAN SEE THIS.

7 A SO THE ZEIGER STUDY IS THE ONE SHOWN AT THE
8 BOTTOM.

9 Q ALL RIGHT.

10 A AND MODEL 1 WAS THE LINEAR MODEL. IT
11 PROVIDED THE BEST FIT, IF WE LOOK IN THE MODEL 1 VERSUS
12 MODEL 2, WHICH IS SHOWN TO THE RIGHT.

13 Q OVER HERE?

14 A THE WEIGHT OF EVIDENCE WOULD SUGGEST THAT
15 THERE IS FOUR TIMES -- THE FIT OF THE LINEAR MODEL WAS
16 FOUR TIMES BETTER THAN A SIMPLE CURVATURE MODEL, WHICH IS
17 MY MODEL 2, SUGGESTING THAT SOMETHING IS GOING ON AT
18 HIGHER DOSES.

19 Q IS THAT THE 3.75 FIGURE HERE?

20 A 3.75.

21 Q EXPLAIN THAT AGAIN, WHAT DOES THAT SHOW?

22 A IT SHOWS THERE IS NO CURVATURE IN THE
23 RELATIONSHIP, SO AS THE DOSES GET HIGHER, YOU DON'T SEE
24 ANY PLATEUING. YOU DON'T SEE AN INCREASE.

25 Q OKAY.

26 A THE THIRD ONE, WHICH IS MOST PERTINENT IS
27 COMPARING THE THRESHOLD MODEL WITH THE LINEAR MODEL. THE
28 LINEAR MODEL HAS A WEIGHT OF EVIDENCE 873,000 TIMES

1 GREATER THAN THE THRESHOLD MODEL.

2 Q SO THE LINEAR MODEL IS STATISTICALLY 873,182
3 TIMES GREATER THAN THE THRESHOLD MODEL?

4 A YES, THE WEIGHT OF EVIDENCE FAVORING A
5 LINEAR MODEL IS 873,000 TIMES STRONGER THAN THE THRESHOLD
6 MODEL.

7 Q THAT IS BASED UPON THE A.I.C.C. STATISTIC?

8 A YES.

9 Q WHICH YOU DESCRIBED EARLIER, AKAIKE'S
10 INFORMATION CRITERIA?

11 A AKAIKE INFORMATION CRITERIA.

12 Q WHICH I THINK YOU TOLD US IS GENERALLY
13 ACCEPTED FOR A VERY STRONG MODEL FOR GOODNESS OF FIT?

14 A YES, IT IS. IT IS VERY WIDELY ACCEPTED.

15 Q DID ZEIGER IN HIS PAPER USE SUCH GOODNESS OF
16 FIT MODELS?

17 A NO. IF THEY HAD, THEY WOULD NOT HAVE COME
18 TO THE CONCLUSION THAT THEY DID.

19 MR. SCHURZ: OBJECTION; CALLS FOR SPECULATION.
20 LACKS FOUNDATION AS TO WHAT THE ZEIGER INVESTIGATORS
21 WOULD HAVE DONE. THEY PUBLISHED A PEER-REVIEWED ARTICLE
22 AND CAME TO A CONCLUSION.

23 THE COURT: OVERRULED.

24 MR. METZGER: THANK YOU VERY MUCH, DR. RAPPAPORT.
25 NO FURTHER QUESTIONS.

26 MR. SCHURZ: ONE VERY SHORT QUESTION, JUST TO CLEAR
27 UP SOMETHING.

28

1 RECCROSS-EXAMINATION

2
3 BY MR. SCHURZ:4 Q DR. RAPPAPORT, YOU TESTIFIED THAT THERE HAVE
5 BEEN NO PUBLISHED REPORTS OF IN VIVO MEASUREMENT IN
6 HUMANS OF D.N.A. ADDUCTS FROM ACRYLAMIDE EXPOSURE?

7 A I THINK I SAID I WAS NOT AWARE OF ANY.

8 Q THANK YOU.

9 A I AM NOT AWARE OF ANYONE WHO HAS ACTUALLY
10 TRIED TO MEASURE THEM.

11 THE COURT: OKAY. NO MORE QUESTIONS.

12 MAY THE WITNESS BE EXCUSED?

13 MR. METZGER: YES.

14 MR. SCHURZ: YES, YOUR HONOR.

15 THE COURT: DR. RAPPAPORT MAY BE EXCUSED.

16 MR. SCHURZ: YOUR HONOR, WITH RESPECT TO THIS
17 WITNESS, WE WOULD RESERVE OUR RIGHT TO STRIKE THOSE
18 PORTIONS OF HIS TESTIMONY RELYING ON THE N.C.A. DATA AS
19 LACKING IN FOUNDATION, WITH RESPECT TO THAT REPORT AND
20 HIS RELIANCE ON WHAT HE HAS REFERRED TO AS "GROUP DATA."
21 WE WOULD LIKE TO PROVIDE YOU SOMETHING IN WRITING WITH
22 RESPECT TO THAT.

23 THE COURT: ALL RIGHT.

24 DR. RAPPAPORT, YOU MAY STEP DOWN.

25 WHAT IS THE SCHEDULE FOR TOMORROW?

26 MR. METZGER: TOMORROW IS DR. FRAZIER.

27 THE COURT: HOW LONG IS DR. FRAZIER GOING TO TAKE
28 TOMORROW?

1 MR. METZGER: I EXPECT I WILL FINISH WITH HIM
2 PROBABLY BY NOON, I WOULD EXPECT.

3 THE COURT: BY NOON. OKAY. HOW LONG IS CROSS-
4 EXAMINATION?

5 MR. SCHURZ: MR. CALIA WILL BE DOING THAT, AND HE
6 IS NOT HERE, SO I AM LOATHE TO MAKE PREDICTIONS AS TO
7 WHAT HE HAS PLANNED.

8 THE COURT: I HAVE TO CONCLUDE BY 3:30 TOMORROW. I
9 JUST WANT TO, DEPENDING ON HOW LONG YOU ANTICIPATE, I
10 WOULD START THE AFTERNOON SESSION AT 1:00 O'CLOCK INSTEAD
11 OF 1:30 IF YOU NEED EXTRA TIME IN ORDER TO CONCLUDE BY
12 3:30 OR BEFORE.

13 MR. SCHURZ: ALL RIGHT.

14 MR. METZGER: WHEN I SAY I WILL FINISH BY NOON, I
15 THINK I WILL ACTUALLY BE DONE BY A BIT, SO I THINK WE
16 WILL BE ALL RIGHT.

17 MS. CORASH: YOUR HONOR, ONE ADDITIONAL SCHEDULING
18 REQUEST. RIGHT NOW THE COURT IS DARK ALL DAY THURSDAY OR
19 AT LEAST WE ARE NOT IN SESSION ALL DAY THURSDAY BECAUSE
20 MR. METZGER HAS A HEARING ON THURSDAY MORNING. IF WE CAN
21 CONCLUDE WITH DR. FRAZIER TOMORROW, THE ONLY REASON WE
22 WOULD BE BACK HERE ON FRIDAY WOULD BE FOR PLAINTIFF TO
23 READ P.M.K. TESTIMONY INTO THE RECORD.

24 WE HAVE OFFERED TO STIPULATE TO THE FACTS
25 THAT ARE -- THAT EMERGE FROM THE DESIGNATED TESTIMONY. I
26 HAVE NOT BEEN ABLE TO GET A RESPONSE FROM PLAINTIFF. IF
27 I COULD JUST MAKE A SUGGESTION.

28 THE COURT: I HAVE A BETTER SUGGESTION, I DON'T

1 KNOW WHERE YOU ARE GOING, I AM SORRY TO BE INTERRUPTING,
2 BUT WHY DON'T -- INSTEAD OF READING IT, WHY DON'T YOU
3 JUST OUTLINE AND SUBMIT AN EXHIBIT WHAT YOU WANT TO READ
4 AND I WILL RULE ON IT AND READ IT AND MARK IT AS AN
5 EXHIBIT IF YOU WANT A RECORD OF IT. WE DON'T HAVE TO
6 WASTE TIME READING IT.

7 MS. CORASH: THAT WOULD BE FINE. WE WOULD LIKE TO
8 AVOID HAVING TO BE HERE ON FRIDAY MORNING. SOME OF US
9 WOULD LIKE TO GET HOME BY SUNSET AND THERE IS NO REASON
10 FOR IT SINCE WE CAN EITHER STIPULATE OR PROCEED AS THE
11 COURT HAS SUGGESTED, OR WE CAN DO THIS THURSDAY
12 AFTERNOON. THERE IS NO REASON THAT WE COULD NOT PROCEED
13 ON THURSDAY --

14 THE COURT: WHATEVER THE SCHEDULE, THERE IS NO
15 REASON TO START READING TESTIMONY WHERE YOU COULD JUST
16 SUBMIT A TRANSCRIPT.

17 MR. METZGER: YOUR HONOR, HERE IS MY ONLY CONCERN:
18 I AM CONCERNED THAT WE HAVE A REPORTER'S TRANSCRIPT THAT
19 INCLUDES ALL THE TESTIMONY. EXHIBITS ARE TYPICALLY
20 RETURNED TO COUNSEL AT THE END OF A TRIAL AND ARE NOT IN
21 THE RECORD. IF -- I HOPE THIS IS NOT GOING TO GO UP ON
22 APPEAL, BUT IF IT DOES, I THINK WE NEED TO HAVE THE
23 TESTIMONY IN THE REPORTER'S TRANSCRIPT TO HAVE AN
24 ACCURATE AND COMPLETE RECORD.

25 THE COURT: IF YOU WANT AN ACCURATE RECORD, YOU ARE
26 GOING TO INCLUDE EXHIBITS OR ARE YOU GOING TO DEPRIVE THE
27 APPELLATE COURT OF THE EXHIBITS?

28 MR. METZGER: I ACTUALLY HAVE NOT DONE APPEALS WITH

1 THE EXHIBITS AS PART OF THE RECORD.

2 THE COURT: IT IS A VERY SIMPLE PROCESS. I
3 UNDERSTAND YOU DON'T WANT JUST TO SUBMIT THE TRANSCRIPT
4 TO THE COURT AND SAY THAT THE COURT SHOULD READ PAGES 100
5 TO 150 BECAUSE YOU DON'T KNOW WHAT HAPPENS WITH THAT, AND
6 YOU DON'T KNOW WHAT HAPPENS AT THE COURT OF APPEAL, BUT
7 IF YOU MARKED AN EXHIBIT, THIS IS THE TESTIMONY THAT I
8 WANT READ, AND THE COURT ACCEPTS THAT TESTIMONY, PAGES
9 100 TO 150 AND WE MARK IT AS EXHIBIT 1000, AND IT IS IN
10 THE RECORD AS AN EXHIBIT, WHAT IS THE PROBLEM WITH IT?

11 MR. METZGER: LET ME --

12 THE COURT: DO YOU THINK IT IS WORTHWHILE JUST
13 SITTING AROUND READING HERE OR ARE YOU GOING TO HAVE AN
14 ACTOR DO SOME DRAMATIC RECITATIONS OR NOT?

15 MR. METZGER: NOTHING IN THIS CASE IS DRAMATIC. I
16 THINK YOU KNOW THAT BY NOW. THIS IS NOT -- THERE IS NO
17 SEX OR DRUGS OR ANYTHING OF INTEREST IN THIS CASE.

18 THE COURT: WHO IS THAT GUY ON PUBLIC TELEVISION,
19 THE SCIENCE GUY?

20 MR. METZGER: LET ME THINK ABOUT IT. I DON'T WANT
21 TO WASTE TIME.

22 THE COURT: I DO AGREE WITH MS. CORASH, WE DON'T
23 NEED TO COME IN FRIDAY MORNING TO READ DEPOSITIONS.

24 MR. METZGER: VERY GOOD. THEN WE WILL FINISH
25 TOMORROW WITH DR. FRAZIER AND THEN WE WILL BE BACK ON
26 MONDAY.

27 THE COURT: LET'S RESOLVE THIS DEPOSITION TESTIMONY
28 ISSUE BY -- I WILL ASK COUNSEL TO MEET AND CONFER, SEE IF

1 YOU CAN RESOLVE IT. YOU KNOW WHAT YOU WANT TO READ INTO
2 THE RECORD. COUNSEL FOR THE DEFENSE WOULD OBJECT TO
3 PORTIONS. I WILL MAKE RULINGS AND THE REST I COULD READ.

4 MR. METZGER: I THINK THAT SOUNDS FINE.

5 THE COURT: FOR MYSELF.

6 MR. METZGER: I THINK THAT SOUNDS FINE.

7 THE COURT: ONE OTHER THING, I ASKED COUNSEL TO
8 UPDATE THE LIST OF EXHIBITS, AND I DON'T KNOW IF YOU HAVE
9 DONE THAT, BUT I WOULD ASK THAT RATHER THAN SUBMIT AN OLD
10 ONE FROM LAST WEEK, YOU MIGHT AS WELL UPDATE IT THROUGH
11 TODAY.

12 MR. METZGER: RIGHT.

13 THE COURT: THANK YOU.

14 MR. METZGER: THANK YOU, YOUR HONOR.

15

16 (THE MATTER WAS ADJOURNED AT 4:14 P.M.)

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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT 323

HON. ELIHU M. BERLE, JUDGE

COUNCIL FOR EDUCATION AND RESEARCH ON)
TOXICS, A CALIFORNIA CORPORATION,)

PLAINTIFF,)

VS.)

CASE NO.
BC435759

STARBUCKS CORPORATION, A CALIFORNIA)
CORPORATION, ET AL.,)

DEFENDANTS.)

AND CONSOLIDATED ACTION.)

_____)

I, KAREN VILICICH, CSR NO. 7634, OFFICIAL
COURT REPORTER OF THE SUPERIOR COURT OF THE STATE OF
CALIFORNIA, FOR THE COUNTY OF LOS ANGELES, DO HEREBY
CERTIFY THAT THE FOREGOING PAGES 151 THROUGH 223 COMPRISE
A FULL, TRUE AND CORRECT TRANSCRIPT OF THE TESTIMONY AND
PROCEEDINGS HELD IN THE ABOVE-ENTITLED MATTER ON TUESDAY,
SEPTEMBER 30, 2014.

DATED THIS 30TH DAY OF SEPTEMBER, 2014.

KAREN VILICICH, CSR NO. 7634
OFFICIAL REPORTER PRO TEMPORE

EXHIBIT “F”

4/14/2014

STEPHEN M. RAPPAPORT
Curriculum Vitae

Personal Information:

Address: [REDACTED], CA [REDACTED]
Telephone: (510) [REDACTED] (H); (510) 942-4355 (W)
E-mail: srappaport@berkeley.edu
Born: January 6, 1948 in San Antonio, TX
Marital Status: Married to Patricia O. Rappaport
Citizenship: U.S.A.

Education:

University	Location	Dates	Major	Degree
University of Illinois	Urbana, IL	9/67-6/69	Chemistry	BS
University of North Carolina	Chapel Hill, NC	8/71-8/74	Environmental Sci. & Engineering	MSPH (1973) PhD (1974)

Experience:

Dates	Position	Description
2006- Present	Professor of Environmental Health , Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, CA Director , Center for Exposure Biology, a multidisciplinary center to develop state-of-the-art biomarkers and biosensors, with faculty from Public Health, Chemistry, and Engineering.	Graduate-level teaching and research in environmental health. Research interests: profiling biomarkers in studies of human exposure, investigating relationships between chemical exposures and biomarker levels, statistical approaches for evaluating exposures, developing state-of-the-art methods for measuring macromolecular adducts in biological samples.
1990 – 2006	Professor of Environmental Health , Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina, Chapel Hill, NC Program Director , NIOSH Educational Resource Center (1990-1995) Project Director , NIEHS Training Grant component for Environmental Exposure Assessment (1994- 2008) Core Director , Exposure-Biomarkers Research Core, NIEHS Center for Environmental Health and Susceptibility (2001-2008)	Graduate-level teaching and research in occupational and environmental health. Main areas of interest included biomonitoring and assessment of chemical exposures. Established graduate curriculum in <i>Exposure Assessment and Control</i> . Assisted in developing Program-Project (SBRP) Grant, Center Grant, and Training Grant, all funded by NIEHS.
1976 - 1990	Professor of Occupational Health (1989-1990); Associate Professor (1982-1989); Assistant Professor (1976-1982), School of Public Health, University of California, Berkeley, CA Program Director (1985-1990), Health Effects Component of the Toxic Substances Research and Teaching Program	Graduate-level teaching and research in occupational and environmental health. Developed methods for assessing human exposures to toxic chemicals and the resulting doses received over time. Initiated the Health Effects Component of the University of California's Toxic Chemicals Research and Teaching Program.
1974 - 1976	Staff Member , University of California, Los Alamos National Laboratory, Los Alamos, NM	Developed air sampling and analytical methods for organic carcinogens.
1971- 1974	Occupational Health Trainee , Department of Environmental Sciences and Engineering,	PhD dissertation involved the chemical identification of effluents from rubber

	<i>University of North Carolina, Chapel Hill, NC</i>	vulcanization.
1969 - 1971	Analytical Chemist , <i>Hazleton Laboratories, Inc., Environmental Sciences Laboratory, Vienna, VA</i>	Analyzed pesticide residues, organic solvent vapors, and trace metals in various environmental media.

Visiting Appointments:

Visiting Honorary Research Fellow, London School of Hygiene and Tropical Medicine, University of London, UK (1983-1984)

Visiting Scientist, Dept. of Occupational and Environmental Medicine, Gothenburg University, Gothenburg, Sweden (1994)

Visiting Scientist, INSERM U190, Environmental and Occupational Epidemiology, Paris, France (1995)

Visiting Scientist, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

Visiting Honorary Research Fellow, Institute for Occupational Medicine, Edinburgh, Scotland (2000-2001)

Visiting Professor, Institute for Risk Assessment Science, Utrecht University, the Netherlands (2001)

Visiting Researcher, Institute for Occupational Health (AMI), Copenhagen, Denmark (2001)

Visiting Scientist, Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD (2003)

Welcome Trust Fellow, Dept. of Epidemiology and Biostatistics, Imperial College, London, U.K. (2012)

Senior Visiting Scientist, International Agency for Research on Cancer, Lyon, France (2013)

Professional Societies:

American Association for Cancer Research

American Society for Exposure Science

British Occupational Hygiene Society

American Academy of Industrial Hygiene

American Conference of Governmental Industrial Hygienists

Alpha Chi Sigma (Professional Chemistry)

National and International Service:

Member, Standing Committee on Emerging Science for Environmental Health Decisions, U.S. National Academy of Sciences (2008-2012)

Editorial Board: *Occupational and Environmental Medicine* (since 2004)

Editorial Board: *Biomarkers: Biochemical Indicators of Exposure, Response and Susceptibility to Chemicals* (since 1995)

North American Editor, *Annals of Occupational Hygiene* 1997 - 2006

Member of PhD Jury for Lode Godderis (Dept. of Industrial Hygiene and Toxicology, Catholic University of Leuven, Leuven Belgium, 2006)

Editorial Board: *Journal of Occupational Health* (1999-2005)

External Advisory Committee, Kresge Center for Environmental Health, Harvard University (1997 - 2002)

Consultant on Exposure Assessment, Center to Protect Workers' Rights (since 1996)

Environmental Health Committee, International Council on Metals and the Environment (2001 - 2002)

Opponent for PhD defense of Igor Burstyn (Institute for Risk Assessment Science, Utrecht University, The Netherlands, 2001)

External PhD Examiner for Martine Barnes (Chemistry Dept., Newcastle University, UK, 2001)

Review panel on the health effects of styrene, Harvard Center for Policy Analysis, 2000 - 2001

Board of Overseas Editors, *Annals of Occupational Hygiene* (1987 - 1997)

Promoter for PhD ceremony of Hans Kromhout (Dept. of Air Pollution, Wageningen University, The Netherlands, 1995)

American Industrial Hygiene Association, Awards Committee (1994 - 1995)

Consultant to the Environmental Health Committee, Science Advisory Board, U.S. EPA (1984 - 1991)

Member, Safety and Occupational Health Study Section, NIH/DIRG (1985-1989)
 Member of Acute-Toxics Subcommittee, Science Advisory Board, U.S. EPA (1985 – 1987)
 Editorial Board, *American Industrial Hygiene Association Journal* (1984 – 1986)
 American Industrial Hygiene Association, Exposure Assessment Strategies Committee (1986 – 1987)
 American Academy of Industrial Hygiene, Association Peer Review Committee (1983 – 1985)

Fellowships, Certifications and Awards:

ABIH Certified Industrial Hygienist (Comprehensive Practice, since 1977)
 U.S. Air Force Summer Faculty Research Fellowship, Brooks AFB, TX (1979)
 University of California Regents Fellowship, U.C. Berkeley (1980)
 Award presented by Michigan Industrial Hygiene Society for the most outstanding paper published in *Am Ind Hyg Assoc J* in 1981 (Pub. No. 15)
 Best Speaker Award; Presented by the ACGIH for the best presentation at a sponsored symposium (1988)
 Keenan Research Sabbatical Fellowship, University of North Carolina, Chapel Hill, NC (2000-2001)
 Best Paper Award presented by the Occupational Health Section of the Society for Toxicology, 2001 (Publ. No. 107)
 Distinguished Lecturer, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, 2008
 Jerome J. Wesolowski Award for sustained and outstanding contributions to the knowledge and practice of human exposure assessment, awarded by the International Society of Exposure Science, 2010
). My paper entitled, Implications of the Exposome on Exposure Science, was

Award for most downloaded paper in 2013, *J Expo Science Environ Epidemiol*, Nature Publishing

Group

Welcome Trust Visiting Scientist Award, Imperial College, London, 2012
 Visiting Senior Scientist Award, International Agency for Research on Cancer, Lyon, France, 2013
 The Centennial Whittenberger Lecturer, Department of Environmental Health, Harvard School of Public Health, Boston, MA, Dec. 6, 2013
 Award for most downloaded paper in 2013, *J Expo Science Environ Epidemiol*, Nature Publishing Group

Ph.D. Dissertations Supervised:

1. Richard D. Knarr, *Air Sampling and Analytical Method for Volatile Thiols*. University of California, Berkeley, 1980.
2. Edward T. Zellers, *Chemical Sensors Based on Coated Ultrasonic Oscillators*. University of California, Berkeley, 1987.
3. Marcie A. Francis, *Time Series Analysis of Occupational Exposure Data*. University of California, Berkeley, 1988.
4. Elin W. H. Kure, *Simulation of Styrene-7,8-Oxide Disposition in Man Following Occupational Exposures to Styrene*. University of California, Berkeley, 1989.
5. Penelope Compton-Quintana, *Use of the Glycophorin A Human Mutation Assay to Study Workers Exposed to Styrene*. University of California, Berkeley, 1990.
6. Myrto X. X. Petreas, *Use of Breath Monitoring in Assessing Exposures to Volatile Organic Solvents*. University of California, Berkeley, 1990.
7. Martha A. Waters, *Some Statistical Considerations in Chemical Exposure Assessment*. University of California, Berkeley, 1990.
8. Tai W. D. Ting, *Development of Methods for Measuring Styrene-Oxide-Protein Adducts in Blood*. University of California, Berkeley, 1990.

9. Thomas A. McDonald, *Protein Adducts of Benzoquinone and Benzene Oxide: a Study of the Reactive Metabolites of Benzene*. University of North Carolina, Chapel Hill, 1994.
10. Rong C. Yu, *Pulmonary Clearance and Retention of Particles in Rats: A Michaelis-Menten Like Kinetic Model*. University of North Carolina, Chapel Hill, 1996.
11. Po-Hsiung Lin, *Disposition of Reactive Metabolites of Pentachlorophenol Based upon Measurements of Protein Adducts*. University of North Carolina, Chapel Hill, 1996.
12. Elaine Symanski, *An Investigation of Time-Dependent Sources of Variation in Occupational Exposure*. University of North Carolina, Chapel Hill, 1996.
13. Karen Yeowell-O'Connell, *Protein Adducts of the Epoxide Metabolites of Styrene and Benzene as Biomarkers of Exposure*. University of North Carolina, Chapel Hill, 1997.
14. Andrew L. Lindstrom, *The Formation and Disposition of Benzene Oxide: Protein Adducts as Indicators of Exposure and Tissue Dose*. University of North Carolina, Chapel Hill, 1999.
15. Melissa A. Troester, *In Vivo Stability of Protein Adducts Formed from Biologically Reactive Electrophiles*. University of North Carolina, Chapel Hill, 2001.
16. Rogelio Tornero-Velez, *Styrene-7,8-Oxide Exposure in Reinforced-Plastic Workers: Bioavailability and Contribution to Dose*. University of North Carolina, Chapel Hill, 2001.
17. Peter Egeghy, *Relationships between Concentrations in Environmental and Alveolar Air: Benzene and Naphthalene*. University of North Carolina, Chapel Hill, 2001.
18. Chin-Hsiang Tsai, *Species Differences in Pentachlorophenol Metabolism in Rodents Based Upon Measurement of Protein Adducts*. University of North Carolina, Chapel Hill, 2002.
19. Berrin Serdar, *Urinary Naphthols as Biomarkers of Exposure to Polycyclic Aromatic Hydrocarbons and Jet Fuel*. University of North Carolina, Chapel Hill, 2003.
20. Joachim Pleil, *Assessing Carcinogenic Polycyclic Aromatic Hydrocarbon (PAH) Levels in the Aftermath of the New York World Trade Center Disaster*. University of North Carolina, Chapel Hill, 2004.
21. Sungkyoon Kim, *Benzene Metabolism in Humans: Dose-dependent Metabolism and Interindividual Variability*. University of North Carolina, Chapel Hill, 2006.
22. Jon Sobus, *Biomarkers of Exposure to Polycyclic Aromatic Hydrocarbons*, University of North Carolina, Chapel Hill, 2008.
23. William Funk, *Protein Adducts as Measures of Exposure in Epidemiological Research*, University of North Carolina, Chapel Hill, 2009.
24. Todd Whitehead, *Using Chemicals in House Dust as Measures of Residential Exposure*. University of California, Berkeley, 2011.
25. Ming-Kei Chung, *Design and Applications of Anti Albumin-Adduct Antibodies to Assess Environmental Exposures*, University of California, Berkeley, 2013.

Funded Research as Principal Investigator (since 1990):

Begin date	End date	Title	Agency (Grant No.)	Award
Sep-1990	Sep-1993	Biomarkers of styrene exposure	NIOSH (R01 OH02221 03-05)	\$391,972
Apr-1992	Mar-1994	Development of biomarkers of exposure	NIEHS (P42 ES05948 01-02)	\$356,509
Jan-1993	May-1996	Protocol for exposure assessment	Nickel Prod. Env. Res. Assoc.	\$317,416
Sep-1995	Aug-2000	Biomarkers of styrene oxide	NCI (R01 CA69463 01-04)	\$1,557,090
Mar-1998	Jun-2000	Models of exposure in the construction industry	Center to Protect Workers Rights	\$45,000
Apr-1995	Mar-2000	Development of biomarkers of exposure	NIEHS (P42 ES5948 03-07 Project 2)	\$822,212
Dec-1997	Aug-1999	Adducts of benzene metabolites	Health Effects Institute/NYU	\$76,146
Jan-1999	Jan-2000	Biomarkers of jet fuel	U.S. Air Force (Subcontract)	\$171,401
Sep-2001	Aug-2002	Analyses of benzene biomarkers	NCI (263 MQ 114454)	\$99,823
Apr-2002	Mar-2004	Community exposures following the WTC disaster	NIEHS (P42 ES05948 08-10) (supplement)	\$532,244

Oct-2003	Dec-2005	A nested case-control study of benzoquinone-protein adducts and acute non-lymphocytic leukemia	NCI (contract for biomarker assays)	\$103,194
Apr-2000	Mar-2011	Development and application of biomarkers of exposure	NIEHS (P42 ES5948 08-16 Project 2)	\$3,236,762
May-2003	Jan-2007	Statistical methods for evaluating exposure-biomarker relationships	American Chemistry Council	\$587,250
Aug-2007	Jul-2011	Biological Response Indicators of Environmental Stress Center	NIEHS (1U54ES016115 01-04)	\$4,737,317
Feb-2009	Jan-2012	Protein adducts in fetal dried blood spots as measures of <i>in utero</i> exposures to carcinogens	Children with Cancer Foundation (U.K.)	\$377,931
Sep-2009	Aug-2014	Exposure assessment for childhood leukemia	NIEHS and USEPA (P01ES017172 01-05)	\$1,000,000
July-2009	June-2012	Childhood leukemias and home environmental exposures	NIEHS (R01ES017441 and R01ES009137)	\$465,808
Jun-2010	May 2013	Albumin adducts as measures of total human exposures	American Chemistry Council LRI-4677	\$1,436,608

Peer-reviewed Publications:

(*Indicates Ph.D. or M.S. student; †indicates post-doctoral fellow)

- 1) **S.M. Rappaport** and D.A. Fraser, Gas Chromatographic-Mass Spectrometric Identification of Volatiles Released from a Rubber Stock During Simulated Vulcanization, *Anal Chem* 48:476-481 (1976).
- 2) **S.M. Rappaport** and E.E. Campbell, The Interpretation and Application of O.S.H.A. Carcinogen Standards for Laboratory Operations, *Am Ind Hyg Assoc J* 37:690-696 (1976).
- 3) D.A. Fraser and **S.M. Rappaport**, Health Aspects of the Curing of Synthetic Rubbers, *Environ Health Perspect* 17:45-53 (1976).
- 4) **S.M. Rappaport** and D.A. Fraser, Air Sampling and Analysis in a Rubber Vulcanization Area, *Am Ind Hyg Assoc J* 38:205-210 (1977).
- 5) **S.M. Rappaport** and D.J. Gettemy, The Generation of Aerosols of Carcinogenic Aromatic Amines, *Am Ind Hyg Assoc J* 39:287-294 (1978).
- 6) Y.Y. Wang*, **S.M. Rappaport**, R.F. Sawyer, R.E. Talcott, and E.T. Wei, Direct Acting Mutagens in Automobile Exhaust, *Cancer Lett* 5:39-47 (1978).
- 7) **S.M. Rappaport** and R. Morales, Air-Sampling and Analytical Method for 4,4'-Methylenebis(2-chloroaniline), *Anal Chem* 51:19-23 (1979).
- 8) **S.M. Rappaport**, M.G. Richard*, M.C. Hollstein* and R.E. Talcott, Mutagenic Activity in Organic Wastewater Concentrates, *Environ Sci Technol* 13:957-961 (1979).
- 9) R. Morales, **S.M. Rappaport** and R. Hermes, Air Sampling and Analytical Procedures for Benzidine, 3,3'-Dichlorobenzidine and their Salts, *Am Ind Hyg Assoc J* 40:970-978 (1979).
- 10) **S.M. Rappaport**, M. McCartney* and E.T. Wei, Volatilization of Mutagens from Beef During Cooking, *Cancer Lett* 8:139-145 (1979).
- 11) R. Knarr* and **S.M. Rappaport**, Determination of Methanethiol at PPM Air Concentrations by Gas Chromatography, *Anal Chem* 52:733-736 (1980).
- 12) E.T. Wei, Y.Y. Wang* and **S.M. Rappaport**, Diesel Emissions and the Ames Test: A Commentary, *JAPCA* 30:267-271 (1980).
- 13) **S.M. Rappaport**, Y.Y. Wang*, E.T. Wei, R. Sawyer, B.E. Watkins and H. Rapoport, Isolation and Identification of a Direct-Acting Mutagen in Diesel-Exhaust Particulates, *Environ Sci Technol* 14:1505-1509 (1980).
- 14) R.D. Knarr* and **S.M. Rappaport**, Impregnated Filters for the Collection of Ethanethiol and Butanethiol in Air, *Am Ind Hyg Assoc J* 42:839-841 (1981).

- 15) **S.M. Rappaport**, S. Selvin, R.C. Spear and C. Keil*, Air Sampling in the Assessment of Continuous Exposures to Acutely Toxic Chemicals. Part I- Strategy, *Am Ind Hyg Assoc J* 42:831-838 (1981).
- 16) X.B. Xu, J.P. Nachtman, **S.M. Rappaport**, E.T. Wei, S. Lewis and A.L. Burlingame, Identification of 2-Nitrofluorene in Diesel Exhaust Particulates, *J Appl Toxicol* 1:196-198 (1981).
- 17) J.P. Nachtman, X.B. Xu, **S.M. Rappaport**, R.E. Talcott and E.T. Wei, Mutagenic Activity in Diesel Exhaust Particulates, *Bull Environ Contam Toxicol* 27:463-466 (1981).
- 18) K. Geisling*, R. Miksch and **S.M. Rappaport**, The Generation of Dry Formaldehyde at Trace Levels by the Vapor Phase Depolymerization of Trioxane, *Anal Chem* 54:140-142 (1982).
- 19) X.B. Xu, J.P. Nachtman†, Z.L. Jin, E.T. Wei, **S.M. Rappaport** and A.L. Burlingame, Isolation and Identification of Mutagenic Nitro-PAH in Diesel Exhaust Particulates, *Anal Chim Acta* 136:163-174 (1982).
- 20) **S.M. Rappaport**, Z.L. Jin and X.B. Xu, HPLC with Reductive Electrochemical Detection of Mutagenic Nitro-Substituted Polynuclear Aromatic Hydrocarbons in Diesel Exhausts, *J Chromatog* 240:145-154 (1982).
- 21) **S.M. Rappaport**, R.C. Spear and J.L. Yager, Industrial Hygiene Data: Compliance, Dosage and Clinical Relevance, *West J Med* 137:572-576 (1982).
- 22) K.L. Geisling*, M.K. Tashima, J.R. Girman, R.R. Miksch and **S.M. Rappaport**, A Passive Sampling Device for Determining Formaldehyde in Indoor Air, *Environ Internat* 8:153-158 (1982).
- 23) W.H. Bruvold, **S.M. Rappaport**, T.C. Wu, B.E. Bulmer, C.E. DeGrange* and J.M. Kooler, Determination of Nuisance Odor in a Community, *Water Poll Cont Assoc J* 55:229-233 (1983).
- 24) Z.L. Jin and **S.M. Rappaport**, Microbore Liquid Chromatography with Electrochemical Detection for Determination of Nitro-Substituted Polynuclear Aromatic Hydrocarbons in Diesel Soot, *Anal Chem*, 55:1778-1781 (1983).
- 25) **S.M. Rappaport**, The Rules of the Game: An Analysis of OSHA's Enforcement Strategy, *Am J Ind Med*, 6:29-303 (1984).
- 26) **S.M. Rappaport**, W. Cameron* and S. McAllister*, Outgassing of Ethylene Dibromide from Fumigated Oranges, *J Ag Food Chem*, 32:1112-1116 (1984).
- 27) D. Fluck*, **S.M. Rappaport**, D. Eastmond* and M.T. Smith, Conversion of 1-Naphthol to Naphthoquinone Metabolites by Rat-Liver Microsomes: Demonstration by High Pressure Liquid Chromatography with Electrochemical Detection, *Arch Biochem Biophys*, 235:351-358 (1984).
- 28) **S.M. Rappaport**, Smoothing of Exposure Variability at the Receptor: Implications for Health Standards, *Ann Occup Hyg*, 29:201-214 (1985).
- 29) M. T. Smith, D. Fluck*, D. Eastmond*, and **S.M. Rappaport**, Detection of Quinone Metabolites by HPLC with Reductive Electrochemical Detection, *Life Chem Rep*, 3:250-258 (1985).
- 30) S. Selvin, **S.M. Rappaport**, R.C. Spear, J. Schulman*, M. Francis*, A Note on the Assessment of Exposures Using One-Sided Tolerance Limits, *Am Ind Hyg Assoc J* 48:89-93 (1987).
- 31) **S.M. Rappaport** and S. Selvin, A Method for Evaluating the Mean Exposure from a Lognormal Distribution, *Am Ind Hyg Assoc J* 48:374-379 (1987).
- 32) **S.M. Rappaport**, S. Selvin, and M. Waters*, Exposure to Hydrocarbon Components of Gasoline in the Petroleum Industry, *Appl Indl Hyg* 2:148-154 (1987).
- 33) **S.M. Rappaport** and R.C. Spear, Physiological Damping of Exposure Variability During Brief Periods, *Ann Occup Hyg* 32:21-33 (1988).
- 34) S.F. Liu, **S.M. Rappaport**, J. Rasmussen, and W. Bodell, Detection of Styrene-Oxide-DNA Adducts by ³²P Post-Labeling, *Carcinogenesis* 9:1401-1404 (1988).
- 35) **S.M. Rappaport**, R.C. Spear and S. Selvin, The Influence of Exposure Variability on Dose-Response Relationships, *Ann Occup Hyg* 32 (Supl.1): 529-537 (1988).
- 36) **S.M. Rappaport**, S. Selvin, and S.A. Roach, A Strategy for Assessing Exposures Relative to Multiple Limits, *Appl Ind Hyg* 3:310-315 (1988).
- 37) M. Francis*, R.C. Spear, S. Selvin, and **S.M. Rappaport**, The Effect of Autocorrelation on the Estimation of Workers' Daily Exposures, *Am Ind Hyg Assoc J* 50:37-43 (1989).
- 38) S. Selvin and **S.M. Rappaport**, A Note on the Estimation of the Mean Value from a Lognormal Distribution, *Am Ind Hyg Assoc J* 50:627-630 (1990).

- 39) S.A. Roach and **S.M. Rappaport**, But They Are Not Thresholds - A Critical Analysis of the Documentation of Threshold Limit Values, *Am J Ind Med*, 17:727-753 (1990).
- 40) D. Paxman† and **S.M. Rappaport**, Analysis of OSHA's Short-Term-Exposure Limit for Benzene, *Reg Toxicol Pharmacol* 11:275-287 (1990).
- 41) D. Ting*, M.T. Smith, P. Doane-Seltzer and **S.M. Rappaport**, Analysis of Styrene-Oxide-Globin Adducts Based Upon Reaction with Raney-Nickel, *Carcinogenesis* 11:755-760 (1990).
- 42) E. T. Zellers*, R. M. White and **S.M. Rappaport**, Use of a Surface-Acoustic-Wave Sensor to Characterize the Reaction of Styrene Vapor with a Square-Planar Organoplatinum Complex, *Anal Chem* 62:1222-1227 (1990).
- 43) E.T. Zellers*, N. Hassold, R.M. White and **S.M. Rappaport**, Selective Real Time Measurement of Styrene Vapor Using a Surface-Acoustic-Wave Sensor with a Regenerable Organoplatinum Coating, *Anal Chem* 62:1227-1232 (1990).
- 44) D. Ting*, M.T. Smith, P. Doane-Setzer, J. Woodlee, and **S.M. Rappaport**, Measurement of Styrene-Oxide Cysteine Adducts in Hemoglobin by Selective Catalytic Reduction, *Adv Exper Med Biol* 283:837-841 (1990).
- 45) **S.M. Rappaport**, Assessment of Long-Term Exposures to Toxic Substances in Air, *Ann Occup Hyg* 35:61-121 (1991).
- 46) J.C. Robinson, D. G. Paxman† and **S.M. Rappaport**, Implications of OSHA's Reliance Upon TLVs in Developing the Air-Contaminants Standard, *Am J Ind Med* 19:3-13 (1991).
- 47) **S.M. Rappaport**, Selection of the Measures of Exposure for Epidemiology Studies, *Appl Occup Environ Hyg* 6:448-457 (1991).
- 48) **S.M. Rappaport**, E. Kure*, M. Petreas*, D. Ting* and J. Woodlee, A Field Method for Measuring Solvent Vapors in Exhaled Air - Application to Styrene Exposure, *Scand J Work Environ Health* 17:195-204 (1991).
- 49) M. Waters*, S. Selvin and **S.M. Rappaport**, A New Goodness-of-Fit Test for the Lognormal Model Applied to Occupational Exposures, *Am Ind Hyg Assoc J*, 52:493-502 (1991).
- 50) M. Petreas*, **S.M. Rappaport**, B.L. Materna and D.M. Rempel, Mixed Exhaled Air Measurements to Assess Exposure to Tetrachloroethylene in Dry Cleaners, *J Exp Assess Epidem*, Supl. 1: 25-39 (1992).
- 51) P.J.E. Compton-Quintana*, R.H. Jensen, W.L. Bigbee, S.G. Grant, R.G. Langlois, M.T. Smith and **S.M. Rappaport**, Use of the Glycophorin A Human Mutation Assay to Study Workers Exposed to Styrene, *Environ Health Perspect* 99:297-301 (1993).
- 52) **S.M. Rappaport**, TLVs, PELs and Feasibility: The Bases for Exposure Limits in the U.S., *Am J Ind Med* 23: 683-694 (1993).
- 53) **S.M. Rappaport**, Biological Considerations in Assessing Exposures to Genotoxic and Carcinogenic Agents, *Int Arch Occup Environ Health*, 65:S29-S35 (1993).
- 54) **S.M. Rappaport**, D. Ting*, Z.L. Jin, K. Yeowell-O'Connell*, S. Waidyanatha, and T. McDonald*, Application of Raney Nickel to Measure Adducts of Styrene Oxide with Hemoglobin and Albumin, *Chem Res Toxicol* 6: 238-244 (1993).
- 55) H. Kromhout†, E. Symanski*, and **S.M. Rappaport**, A Comprehensive Evaluation of Within- and Between-Worker Components of Occupational Exposure to Chemical Agents, *Ann Occup Hyg* 37: 253-270 (1993).
- 56) J. Yager, W. Paradisin and **S.M. Rappaport**, Sister Chromatid Exchanges in Lymphocytes are Increased in Relation to Longitudinally Measured Occupational Exposure to Low Concentrations of Styrene, *Mutat Res* 19:155-165 (1993).
- 57) **S.M. Rappaport**, H. Kromhout†, and E. Symanski*, Variation of Exposure Between Workers in Homogeneous Exposure Groups, *Am Ind Hyg Assoc J*, 54:654-662 (1993).
- 58) T. McDonald*, S. Waidyanatha, and **S.M. Rappaport**, Measurement of Adducts of Benzoquinone with Hemoglobin and Albumin, *Carcinogenesis* 14:1927-1932 (1993).
- 59) T. McDonald*, S. Waidyanatha, and **S.M. Rappaport**, Production of Benzoquinone Adducts with Hemoglobin and Bone-Marrow Proteins Following Administration of [¹³C₆]benzene to Rats, *Carcinogenesis* 14:1921-1925 (1993).
- 60) S. Waidyanatha, T.A. McDonald*, P.H. Lin*, and **S.M. Rappaport**, Measurement of Hemoglobin and Albumin Adducts of Tetrachlorobenzoquinone, *Chem Res Toxicol* 7:463-468 (1994).

- 61) E. Horvath, K. Pongracz, **S.M. Rappaport**, and W.J. Bodell, ^{32}P -Postlabeling Detection of DNA Adducts in Mononuclear Cells of Workers Occupationally Exposed to Styrene, *Carcinogenesis* 15:1309-1315 (1994).
- 62) E. Symanski* and **S.M. Rappaport**, An Investigation of the Dependence of Exposure Variability on the Interval Between Measurements, *Ann Occup Hyg* 38:361-372 (1994).
- 63) T. A. McDonald*, K. Yeowell-O'Connell* and **S.M. Rappaport**, Comparison of Adducts of Benzene Oxide and Benzoquinone in the Blood and Bone Marrow of Rats and Mice Exposed to [$^{14}\text{C}/^{13}\text{C}$]Benzene, *Cancer Res* 54:4907-4914 (1994).
- 64) **S.M. Rappaport**, E. Symanski*, J.W. Yager, and L.L. Kupper, The Relationship between Environmental Monitoring and Biological Markers in Exposure Assessment, *Environ Health Perspect* 103 (Supl 3): 49-53 (1995).
- 65) M. X. Petreas*, J. Woodlee, C. E. Becker, and **S.M. Rappaport**, Retention of Styrene Following Controlled Exposure to Constant and Fluctuating Air Concentrations, *Int Arch Occup Environ Health* 67:27-34 (1995).
- 66) **S.M. Rappaport**, Biological Monitoring and Standard Setting in the U.S.A.: A Critical Appraisal, *Toxicol Lett* 77:171-182 (1995).
- 67) **S.M. Rappaport**, R. Lyles* and L.L. Kupper, An Exposure-Assessment Strategy Accounting for Within- and Between-Worker Sources of Variability, *Ann Occup Hyg* 39:469-495 (1995).
- 68) B. Järholm and **S.M. Rappaport**, A Model to Estimate the Delivered Doses of Substances in Liquid and Gaseous Phases, *Int J Occup Environ Health* 1:311-314 (1995).
- 69) K. Yeowell-O'Connell*, Z. Jin, and **S.M. Rappaport**, Determination of Albumin and Hemoglobin Adducts in Workers Exposed to Styrene and Styrene Oxide, *Cancer Epid Biom Prev* 5: 205-215 (1996).
- 70) S. Waidyanatha, P. H. Lin*, and **S.M. Rappaport**, Characterization of Chlorinated Adducts of Hemoglobin and Albumin following Administration and of Pentachlorophenol to Rats, *Chem Res Toxicol* 9: 647-653 (1996).
- 71) K. Yeowell-O'Connell*, T. A. McDonald*, and **S.M. Rappaport**: Analysis of Hemoglobin Adducts of Benzene Oxide by Gas-Chromatography-Mass Spectrometry, *Anal Biochem* 237:49-55 (1996).
- 72) R. C. Yu* and **S.M. Rappaport**, Relation between Pulmonary Clearance and Particle Burden, A Michaelis-Menten-Like Model, *Occup Environ Med*, 53:567-572 (1996).
- 73) E. Symanski*, L.L. Kupper, H. Kromhout†, and **S.M. Rappaport**, An Investigation of Systematic Changes in Occupational Exposure, *Am Ind Hyg Assoc J*, 57:724-735 (1996).
- 74) Y. Wang, L.L. Kupper, A. Lof, and **S.M. Rappaport**, Comparison of Average Estimated Metabolic Rates for Styrene in Previously Exposed and Unexposed Groups with Pharmacokinetic Modeling, *Occup Environ Med*, 53:601-605 (1996).
- 75) P. H. Lin*, S. Waidyanatha, and **S.M. Rappaport**, Investigation Of Liver Binding Of Pentachlorophenol Based Upon Measurement Of Protein Adducts, *Biomarkers*, 1:232-243 (1996).
- 76) **S.M. Rappaport**, T. A. McDonald*, and K. Yeowell-O'Connell*: The use of Protein Adducts to Investigate the Disposition of Reactive Metabolites of Benzene, *Environ Health Perspect*, 104(S4):1235-1237 (1996).
- 77) **S.M. Rappaport**, K. Yeowell-O'Connell*, W. Bodell, J. W. Yager, and E. Symanski*, An Investigation of Multiple Biomarkers Among Workers Exposed to Styrene and Styrene-7,8-Oxide, *Cancer Res*, 56:5410-5416 (1996).
- 78) R. H. Lyles*, L. L. Kupper, and **S.M. Rappaport**: A Lognormal Distribution-Based Exposure Assessment Method for Unbalanced Data, *Ann Occup Hyg* 41:63-76 (1997).
- 79) R. H. Lyles*, L. L. Kupper, and **S.M. Rappaport**, Assessing Regulatory Compliance of Occupational Exposures Via the Balanced One-way Random Effects ANOVA Model, *Journal of Agricultural, Biological, and Environmental Statistics* 2:64-86 (1997).
- 80) R. Tornero-Velez*, E. Symanski*, R.C. Yu*, H. Kromhout, and **S.M. Rappaport**: Compliance versus Risk in Assessing Occupational Exposures to Chemicals, *Risk Anal* 17:279-292 (1997).
- 81) R.C. Yu* and **S.M. Rappaport**, A Lung Retention Model based upon Michaelis-Menten-Like Kinetics, *Environ Health Perspect* 105:496-503 (1997).

- 82) A. Lindstrom*, K. Yeowell-O'Connell*, S. Waidyanatha, B. T. Golding, R. Tornero-Velez*, and **S.M. Rappaport**, Measurement of Benzene Oxide in the Blood of Rats Following Administration of Benzene, *Carcinogenesis* 18:1637-1641 (1997).
- 83) P. H. Lin*, S. Waidyanatha, G. Pollack, and **S.M. Rappaport**, Dosimetry of Chlorinated Quinone Metabolites of Pentachlorophenol in the Livers of Rats and Mice Based upon Measurement of Protein Adducts, *Toxicol Appl Pharmacol* 145:399-408 (1997).
- 84) K. Yeowell-O'Connell*, W. Pauwels, M. Severi, Z. Jin, M. R. Walker, **S.M. Rappaport**, and H. Veulemans, Comparison of Styrene-7,8-oxide Adducts Formed Via Reaction with Cysteine, N-terminal Valine, and Carboxylic Acid Residues in Human, Mouse, and Rat Hemoglobin, *Chem Biol Interact* 106:67-85 (1997).
- 85) S. Fustinoni, C. Colosio, A. Colombi, L. Lastrucci, K. Yeowell-O'Connell*, and **S.M. Rappaport**, Albumin and Hemoglobin Adducts as Biomarkers of Exposure to Styrene in Fiberglass-Reinforced Plastics Workers, *Int Arch Occup Environ Health* 71:35-41 (1998).
- 86) R.H. Lyles*, L.L. Kupper, and **S.M. Rappaport**, On Prediction of Lognormal-Scale Mean Exposure Levels in Epidemiologic Studies, *JABES* 2:417-439 (1997).
- 87) E. Symanski*, L.L. Kupper, and **S.M. Rappaport**, A Comprehensive Evaluation of Long-Term Trends in Occupational Exposure. Part 1: Description of the Database, *Occup Environ Med* 55:300-309 (1998).
- 88) E. Symanski*, L. L. Kupper, I. Hertz-Picciotto, and **S.M. Rappaport**, A Comprehensive Evaluation of Long-Term Trends in Occupational Exposure. Part 2: Predictive Models for Declining Exposures, *Occup Environ Med* 55:310-316 (1998).
- 89) A. B. Lindstrom*, K. Yeowell-O'Connell*, S. Waidyanatha, T.A. McDonald*, B. T. Golding, and **S.M. Rappaport**, Formation of Hemoglobin and Albumin Adducts of Benzene Oxide in Mouse, Rat, and Human Blood, *Chem Res Toxicol* 11:302-310 (1998).
- 90) K. Yeowell-O'Connell*, N. Rothman, M. T. Smith, R. B. Hayes, G. Li, S. Waidyanatha, M. Dosemeci, S. Zhang-Yin, N. Titenko-Holland, and **S.M. Rappaport**, Hemoglobin and Albumin Adducts of Benzene Oxide Among Workers Exposed to High Levels of Benzene, *Carcinogenesis* 19:1565-1571 (1998).
- 91) S. Waidyanatha, K. Yeowell-O'Connell*, and **S.M. Rappaport**, A New Assay for Albumin and Hemoglobin Adducts of 1,2- and 1,4-Benzoquinones, *Chem Biol Interact* 115:117-139 (1998).
- 92) P. H. Lin*, S. Waidyanatha, G. M. Pollack, J. A. Swenberg, and **S.M. Rappaport**, Dose-specific Production of Chlorinated Quinone and Semiquinone Adducts in Rodent Livers Following Administration of Pentachlorophenol, *Toxicol Sci*, 47:126-133 (1999).
- 93) L. Nylander-French†, L. L. Kupper, and **S.M. Rappaport**, An Investigation of Factors Contributing to Exposure to Styrene and Styrene-7,8-Oxide in the Reinforced-Plastics Industry, *Ann Occup Hyg*, 43: 99-109 (1999).
- 94) **S.M. Rappaport** and K. Yeowell-O'Connell*, Protein Adducts as Dosimeters of Human Exposure to Styrene, Styrene-7, 8-Oxide, and Benzene, *Toxicol Let*, 108:117-126 (1999).
- 95) **S.M. Rappaport**, M. Weaver*, D. Taylor, L. L. Kupper and P. Susi, Application of Mixed Models to Assess Aerosol Exposures Monitored by Construction Workers During Hot Processes, *Ann Occup Hyg*, 43: 457-469 (1999).
- 96) A. B. Lindstrom, K. Yeowell-O'Connell*, S. Waidyanatha, T. A. McDonald* and **S.M. Rappaport**, Investigation of Benzene Oxide in Bone Marrow and Other Tissues of F344 Rats Following Metabolism of Benzene In Vitro and In Vivo, *Chem Biol Interact*, 122:41-58 (1999).
- 97) M. Troester*, A. B. Lindstrom*, S. Waidyanatha, L. L. Kupper and **S.M. Rappaport**, Stability Of Hemoglobin and Albumin Adducts Of Benzene Oxide and 1,4-Benzoquinone After Administration Of Benzene To F344 Rats, *Toxicol Sci*, 54:88-94 (2000).
- 98) R. Tornero-Velez*, S. Waidyanatha, D. Echeverria, and **S.M. Rappaport**, Measurement of Styrene-7,8-oxide and Other Oxidation Products of Styrene in Air, *J Environ Meas*, 2:111-117 (2000).
- 99) P.P. Egeghy*, R. Tornero-Velez* and **S.M. Rappaport**, Environmental and Biological Monitoring of Benzene during Self-Service Automobile Refueling, *Environ Health Perspect*, 108:1195-1202 (2000).
- 100) S. Waidyanatha, N. Rothman, S. Fustinoni, M.T. Smith, R. B. Hayes, W. Bechtold, M. Dosemeci, G. Li, S. Yin and **S.M. Rappaport**, Urinary Benzene as a Biomarker of Benzene Exposure Among Occupationally-Exposed and Unexposed Subjects, *Carcinogenesis*, 22:279-286 (2001).

- 101) C.H. Tsai*, P.H. Lin*, S. Waidyanatha, and **S.M. Rappaport**, Characterization of Metabolic Activation of Pentachlorophenol to Quinones and Semiquinones in Rodent Liver, *Chem Biol Interact*, 134:55-71 (2001).
- 102) R. Tornero-Velez*, S. Waidyanatha, H. Licea-Pérez*, S. Osterman-Golkar, D. Echeverria and **S.M. Rappaport**, Determination of Styrene and Styrene-7,8-oxide in Human Blood by Gas Chromatography-Mass Spectrometry, *J Chromatog (B)*, 757:59-68 (2001).
- 103) M. A. Weaver*, L.L. Kupper, D. Taylor*, H. Kromhout, P. Susi and **S.M. Rappaport**, Simultaneous Assessment of Occupational Exposures from Multiple Worker Groups, *Ann Occup Hyg*, 45:525-542 (2001).
- 104) M.A. Troester*, L.L. Kupper and **S.M. Rappaport**, Comparison of Nonlinear and Linear Models for Estimating Hemoglobin Adduct Stability, *Biomarkers*, 6:251-261 (2001).
- 105) D. J. Taylor*, L.L. Kupper, **S.M. Rappaport**, and R. H. Lyles, A Mixture Model for Occupational Exposure Data with a Limit of Detection, *Biometrics*, 57:681-688 (2001).
- 106) K. Yeowell-O'Connell*, N. Rothman, S. Waidyanatha, M. T. Smith, R. B. Hayes, G. Li, W. E. Bechtold, M. Dosemeci, L. Zhang, S. Yin and **S.M. Rappaport**, Protein Adducts of 1,4-Benzoquinone and Benzene Oxide among Smokers and Non-smokers Exposed to Benzene in China, *Cancer Epid Biom Prev*, 10: 831-838 (2001).
- 107) R. Tornero-Velez* and **S.M. Rappaport**, Physiological Modeling of the Relative Contributions of Styrene-7,8-oxide Derived from Direct Inhalation and from Styrene Metabolism to the Systemic Dose in Humans, *Toxicol Sci*, 64: 151-161 (2001).
- 108) I. E. Liljelind*, **S.M. Rappaport**, J.O. Levin, A.E. Stromback, A.K. Sunesson and B.G. Jarvholm, Comparison of Self and Expert Assessment of Occupational Exposure to Chemicals, *Scand J Work Environ Health*, 27:311-317 (2001).
- 109) **S.M. Rappaport**, S. Waidyanatha, Q. Qu, R. Shore, X. Jin, B. Cohen, L.-C. Chen, A. A. Melikian, G. Li, S. Yin, H. Yan, B. Xu, R. Mu, Y. Li, X. Zhang, and K. Li, Albumin adducts of Benzene Oxide and 1,4-Benzoquinone as Measures of Human Benzene Metabolism, *Cancer Res*, 62:1330-1337 (2002).
- 110) **S.M. Rappaport**, K. Yeowell-O'Connell*, M. T. Smith, M. Dosemeci, R. B. Hayes, L. Zhang, G. Li, S. Yin and N. Rothman, Non-Linear Production of Benzene Oxide-Albumin Adducts with Human Exposure to Benzene, *J Chromatog (B)*, 778:367-374 (2002).
- 111) P. P. Egeghy*, L. Nylander-French, K. K. Gwin*, I. Hertz-Picciotto, and **S.M. Rappaport**, Self-Collected Breath Sampling for Monitoring Low-Level Benzene Exposures among Automobile Mechanics, *Ann Occup Hyg*, 46: 489-500 (2002).
- 112) J.T. Cohen, G. Carlson, G. Charnley, D. Coggon, E. Delzell, J.D. Graham, H. Greim, D. Krewski, M. Medinsky, R. Monson, D. Paustenbach, B. Petersen, **S.M. Rappaport**, L. Rhomberg, P.B. Ryan, and K. Thompson, A Comprehensive Evaluation of the Potential Health Risks Associated with Occupational and Environmental Exposure to Styrene, *J Toxicol Environ Health B Critical Reviews*, 5: 1-265 (2002).
- 113) M. A. Troester*, A. B. Lindstrom*, S. Waidyanatha, L. L. Kupper, and **S.M. Rappaport**, Stability of Hemoglobin and Albumin Adducts of Naphthalene Oxide, 1,2-Naphthoquinone, and 1,4-Naphthoquinone after Administration of Naphthalene to F344 Rats, *Toxicol Sci*, 68(2): 314-321 (2002).
- 114) S. Waidyanatha, M.A.. Troester*, A.B. Lindstrom*, and **S.M. Rappaport**, Measurement of Hemoglobin and Albumin Adducts of Naphthalene-1,2-oxide, 1,2-Naphthoquinone and 1,4-Naphthoquinone after Administration of Naphthalene to F344 Rats, *Chem Biol Interact*, 141(3): 189-210 (2002).
- 115) Q. Qu, R. Shore, G. Li, X. Jin, L. C. Chen, B. Cohen, A. A. Melikian, D. Eastmond, **S.M. Rappaport**, S. Yin, Y. Li, S. Waidyanatha, K. Li, R. Mu, and X. Zhang, Hematological Changes among Chinese Workers with a Broad Range of Benzene Exposures, *Am J Ind Med*, 42: 275-285 (2002).
- 116) C.-H. Tsai*, P.-H. Lin, S. Waidyanatha, and **S.M. Rappaport**, Fractionation of Protein Adducts in Rats and Mice Dosed with [¹⁴C]Pentachlorophenol, *Arch Toxicol*, 76(11): 628-633 (2002).
- 117) I. Liljelind*, **S.M. Rappaport**, K. Eriksson, J. Andersson, I. A. Bergdahl, A.-L. Sunesson, B. Järholm, Exposure Assessment of Monoterpenes and Styrene - A Comparison of Air Sampling and Biomonitoring, *Occup Environ Med*, 60: 599-603 (2003).
- 118) B. Serdar*, S. Waidyanatha, Y.-X. Zheng, and **S.M. Rappaport**, Simultaneous Determination of Urinary 1- and 2-Naphthols, 3- and 9-Phenanthrols, and 1-Pyrenol in Coke Oven Workers, *Biomarkers*, 8: 93-109 (2003).

- 119) S. Waidyanatha, Y.-X. Zheng, and **S.M. Rappaport**, Determination of Unmetabolized Polycyclic Aromatic Hydrocarbons in Urine of Coke Oven Workers by Headspace Solid Phase Microextraction and Gas Chromatography-Mass Spectrometry, *Chemico-Biol Interact*, 145: 165-174 (2003).
- 120) **S.M. Rappaport**, M. Goldberg, P. Susi, and R. Herrick, Excessive Exposure to Silica in the U.S. Construction Industry, *Ann Occup Hyg*, 47(2): 111-122 (2003).
- 121) P. P. Egeghy*, L. Hauf-Cabalo*, R. Gibson, and **S.M. Rappaport**, Measurement of Benzene and Naphthalene in Air and Breath as Indicators of Exposure to Jet Fuel, *Occ Environ Med*, 60: 969-976 (2003).
- 122) C.-H. Tsai*, P.-H. Lin, M. A. Troester, and **S.M. Rappaport**, The Formation and Removal of Pentachlorophenol-derived Protein Adducts in Rodent Liver under Acute, Multiple and Chronic Dosing Regimens, *Toxicol Sci*, 73: 26-35 (2003).
- 123) B. Serdar*, P. P. Egeghy*, S. Waidyanatha, R. Gibson and **S.M. Rappaport**, Urinary Biomarkers of Exposure to Jet Fuel (JP-8), *Environ Health Perspect*, 111(14): 1760-1764 (2003).
- 124) **S.M. Rappaport** and L. L. Kupper, Variability of Environmental Exposures to Volatile Organic Compounds, *J Exposure Assess Environ Epid*, 14: 82-107 (2004).
- 125) S. Waidyanatha, Y. Zheng, B. Serdar*, and **S.M. Rappaport**, Albumin Adducts of Naphthalene Metabolites as Biomarkers of Exposure to Polycyclic Aromatic Hydrocarbons, *Cancer Epid Biomarkers Prev*, 13 (1): 117-124 (2004).
- 126) R. Vermeulen, G. Li, Q. Lan, M. Dosemeci, **S. M. Rappaport**, X. Bohong, M. T. Smith, L. Zhang, R. B. Hayes, M. Linet, R. Mu, L. Wang, J. Xu, S. Yin, and N. Rothman, Detailed Exposure Assessment for a Molecular Epidemiology Study of Benzene in Two Shoe Factories in China, *Ann Occup Hyg*, 48: 105-116 (2004).
- 127) U. Luderer, R. Tornero-Velez*, T. Shay, **S.M. Rappaport**, N. Heyer, and D. Echeverria, Temporal Association between Serum Prolactin Concentration and Exposure to Styrene, *Occ Environ Med*, 61: 325-333 (2004).
- 128) S. Waidyanatha, N. Rothman, M.T. Smith, R. B. Hayes, M. Dosemeci, G. Li, S. Yin and **S.M. Rappaport**, Rapid Determination of Six Urinary Benzene Metabolites of Occupationally-Exposed and Unexposed Subjects, *Analyt Biochem*, 324: 184-199 (2004).
- 129) J. D. Pleil*, A. Vette, and **S.M. Rappaport**, Assaying Particle-bound Polycyclic Aromatic Hydrocarbons (PAH) from Archived PM2.5 Filters, *J Chromatog (A)*, 1033(1): 9-17 (2004).
- 130) **S. M. Rappaport**, S. Waidyanatha and B. Serdar*, Naphthalene and Its Biomarkers as Surrogates for Exposure to Polycyclic Aromatic Hydrocarbons, *J Environ Monitoring*, 6: 413-416 (2004).
- 131) P. J. Landrigan, P. J. Liroy, G. Thurston., G. Berkowitz, L.C. Chen, S. N. Chillrud, S. H. Gavett, P. G. Georgopoulos, A.S. Geyh, S. Levin, F. Perera, **S.M. Rappaport**, and C. Small, Health and Environmental Consequences of the World Trade Center Disaster, *Environ Health Perspect*, 112: 731-739 (2004).
- 132) B. Serdar*, P. P. Egeghy*, R. Gibson and **S.M. Rappaport**, Dose-Dependent Production of Urinary Naphthols among Workers Exposed to Jet Fuel (JP-8), *Am J Ind Med*, 46: 234-244 (2004).
- 133) J. D. Pleil*, A. Vette, B. Johnson†, and **S.M. Rappaport**, Air Levels of Carcinogenic Polycyclic Aromatic Hydrocarbons Following the World Trade Center Disaster, *PNAS*, 101 (32): 11685-11688 (2004).
- 134) Q. Lan, L. Zhang, G. Li, R. Vermeulen, R.S. Weinberg, M. Dosemeci, **S.M. Rappaport**, M. Shen, B.P. Alter., Y. Wu, W. Kopp, S. Waidyanatha, C. Rabkin, W. Guo, S. Chanock, R.B. Hayes, M. Linet, S. Kim*, S. Yin, N. Rothman, and M.T. Smith, Hematotoxicity in Workers Exposed to Low Levels of Benzene, *Science*, 306: 1776-1776 (2004).
- 135) **S. M. Rappaport**, L. L. Kupper and Y.S. Lin*, On the Importance of Exposure Variability to the Doses of Volatile Organic Compounds, *Toxicol Sci*, 83: 224-236 (2005).
- 136) A. P. Henderson*, M. L. Barnes, C. Bleasdale, R. Cameron, W. Clegg, S. L. Heath, A. B. Lindstrom*, **S.M. Rappaport**, S. Waidyanatha, W. P. Watson and B. T. Golding, Stability of Benzene Oxide and its Reactions with Thiols, *Chem Res Toxicol*, 18: 265-270 (2005).
- 137) **S. M. Rappaport**, S. Waidyanatha, K. Yeowell-O'Connell*, N. Rothman, M.T. Smith, L. Zhang, Q. Qu, R. Shore, G. Li, and S. Yin, Protein Adducts as Biomarkers of Human Benzene Metabolism, *Chem-Biol Interact*, 153-145: 103-109 (2005).

- 138) Q. Lan, L. Zhang, F. Hakim, M. Shen, S. Memon, G. Li, R. Vermeulen, M. T. Smith, **S. M. Rappaport**, R. Hayes, M. Linet, S. Yin and N. Rothman, C. S. Rabkin, Lymphocyte Toxicity and T-Cell Receptor Excision Circles in Workers Exposed to Benzene, *Chem-Biol Interact*, 153-154: 111-115 (2005).
- 139) M. T. Smith, R. Vermeulen, G. Li, L. Zhang, Q. Lan, A. E. Hubbard, M. S. Forrest, C. McHale, X. Zhao, L. Gunn, M. Shen, D. McCarthy, M. McGuire, **S. M. Rappaport**, S. Yin, S. Chanock and N. Rothman, Use of “Omic” Technologies to Study Humans Exposed to Benzene, *Chem-Biol Interact*, 153-154: 123-127 (2005).
- 140) L. Zhang, Q. Lan, W. Guo, G. Li, W. Yang, A. E. Hubbard, R. Vermeulen, **S. M. Rappaport**, S. Yin, N. Rothman and M. T. Smith, Use of OctoChrome Fluorescence in situ Hybridization to Detect Specific Aneuploidy Among all 24 Chromosomes in Benzene-exposed Workers, *Chem-Biol Interact*, 153-154: 117-122 (2005).
- 141) S. Waidyanatha, R. Sangaiah, and **S. M. Rappaport**, Characterization and Quantification of Cysteinyl Adducts of Benzene Diolepoxide, *Chem Res Toxicol*, 18: 1178-1185 (2005).
- 142) Y. S. Lin†, L.L. Kupper, and **S. M. Rappaport**, Air Samples Versus Biomarkers for Epidemiology, *Occ Env Med*, 62: 750-760 (2005).
- 143) R. Wu†, S. Waidyanatha, A. P. Henderson, B. Serdar*, Y. Zheng, and **S. M. Rappaport**, Determination of dihydroxynaphthalenes in human urine by gas chromatography–mass spectrometry, *J Chromatog (B)*, 826: 206-213 (2005).
- 144) A. P. Henderson†, S. Waidyanatha, K. Delany, A. B. Lindstrom, C. Bleasdale, W. P. Watson, **S. M. Rappaport**, and B. T. Golding, Evidence for the Formation of Michael Adducts from (*E,E*)-Muconaldehyde with Thiols Including Glutathione, *Biorganic Chem*, 33(5): 363-373 (2005).
- 145) B. A. Johnson†, L. L. Kupper, D. J. Taylor, and **S. M. Rappaport**, Modeling Exposure-Biomarker Relationships: Applications of Linear and Nonlinear Toxicokinetics for Understanding Genotoxic Metabolism and Carcinogenesis, *J Ag Bio Environ Stat*, 10(4): 440-459 (2005).
- 146) Q. Lan, L. Zhang, M. Shen, M. T. Smith, G. Li, R. Vermeulen, **S. M. Rappaport**, M. S. Forrest, R. B. Hayes, M. Linet, M. Dosemeci, B. P. Alter, R. S. Weinberg, S. Yin, M. Yeager, R. Welch, S. Waidyanatha, S. Kim*, S. Chanock, N. Rothman, Polymorphisms in Cytokine and Cellular Adhesion Molecule Genes and Susceptibility to Hematotoxicity Among Workers Exposed to Benzene, *Cancer Res*, 65(20): 9574-9581 (2005).
- 147) Y.S. Lin†, W. McKelvey*, S. Waidyanatha, and **S. M. Rappaport**, Variability of Albumin Adducts of 1,4-Benzoquinone, a Toxic Benzene Metabolite, in Volunteer Subjects, *Biomarkers*, 11(1): 14-27 (2006).
- 148) Y.-C. E. Chao*, L. L. Kupper, B. Serdar†, P. P. Egeghy*, **S. M. Rappaport**, and L. Nylander-French, Dermal Exposure to Jet Fuel JP-8 Significantly Contributes to the Production of Urinary Naphthols in Fuel-Cell Maintenance Workers, *Environ Health Perspect*, 114(2): 182-185 (2006).
- 149) S. Kim*, R. Vermeulen, S. Waidyanatha, B. Johnson†, Q. Lan, N. Rothman, M. T. Smith, G. Li, L. Zhang, M. Shen, S. Yin, and **S. M. Rappaport**, Using Urinary Biomarkers to Elucidate Dose-Related Patterns of Human Benzene Metabolism, *Carcinogenesis*, 27(4): 772-781 (2006).
- 150) J. D. Pleil*, W. F. Funk*, and **S. M. Rappaport**, Residual Indoor Contamination from World Trade Center Rubble Fires as Indicated by Polycyclic Aromatic Hydrocarbon (PAH) Profiles, *Environ Sci Technol*, 40: 1172-1177 (2006).
- 151) M. Shen, Q. Lan, L. Zhang, S. Chanock, G. Li, R. Vermeulen, **S. M. Rappaport**, W. Guo, R. B. Hayes, M. Linet, S. Yin, M. Yeager, R. Welch, M. S. Forrest, N. Rothman, M. T. Smith, Polymorphisms in Genes Involved in Genome Maintenance Confer Susceptibility to Benzene-Induced Hematotoxicity, *Carcinogenesis*, 27(10): 2083-2089 (2006).
- 152) K. Yokley, H. T. Tran, K. Pekari, **S. M. Rappaport**, V. Riihimaki, N. Rothman, S. Waidyanatha, and P. M. Schlosser, Physiologically Based Pharmacokinetic Modeling of Benzene in Humans: A Bayesian Approach, *Risk Anal*. 26(4): 925-943 (2006).
- 153) B. Serdar†, R. Tornero-Velez*, D. Echeverria, L. Nylander-French, L. L. Kupper, and **S. M. Rappaport**, Predictors of Occupational Exposure to Styrene and Styrene-7,8-Oxide in the Reinforced Plastics Industry, *Occ Environ Med*, 63: 707-712 (2006).

- 154) S. Kim*, R. Vermeulen, S. Waidyanatha, B. A. Johnson†, Q. Lan, M. T. Smith, G. Li, L. Zhang, M. Shen, S. Yin, N. Rothman, and **S. M. Rappaport**, Modeling Human Metabolism of Benzene Following Occupational and Environmental Exposures, *Cancer Epidemiol Biomarkers Prev*, 15(11): 2246-2252 (2006).
- 155) R. Vermeulen, Q. Lan, G. Li, **S. M. Rappaport**, S. Kim, B. van wendel de Joode, M. Shen, X. Bohong, M.T. Smith, L. Zhang, S. Yin, and N. Rothman, Assessment of Dermal Exposure to Benzene and Toluene in Shoe Manufacturing by Activated Carbon Cloth Patches, *J Environ Monit*, 8(11): 1143-1148 (2006).
- 156) D. Meeker, D. B. Barr, B. Serdar†, **S. M. Rappaport**, and R. Hauser, Utility of 1-Naphthol and 2-Naphthol Levels to Assess Environmental Carbaryl and Naphthalene Exposure in an Epidemiology Study, *J Expo Sci Environ Epidemiol*, 17(4): 314-320 (2007).
- 157) Y.S. Lin†, R. Vermeulen, C. Tsai†, S. Waidyanatha, Q. Lan, N. Rothman, M.T. Smith, L. Zhang, M. Shen, G. Li, S. Yin, S. Kim*, and **S. M. Rappaport**, Albumin Adducts of Electrophilic Benzene Metabolites in Benzene-exposed and Control Workers, *Environ Health Perspect*, 28(1): 28-34 (2007).
- 158) J. D. Pleil, D. Kim, J. D. Prah and **S.M. Rappaport**, Exposure Reconstruction for Reducing Uncertainty in Risk Assessment: Example Using MTBE Biomarkers and a Simple Pharmacokinetic Model, *Biomarkers*, 12(4): 331-348 (2007).
- 159) S. Kim*, Q. Lan, S. Waidyanatha, S. Chanock, B. Johnson†, R. Vermeulen, M. T. Smith, L. Zhang, G. Li, M. Shen, S. Yin, N. Rothman and **S. M. Rappaport**, Genetic Polymorphisms and Benzene Metabolism in Humans Exposed to a Wide Range of Air Concentrations, *Pharmacogenetics and Genomics*, 17(10):789-801 (2007).
- 160) B. A. Johnson† and **S. M. Rappaport**, On Modeling Metabolism-Based Biomarkers of Exposure: A Comparative Analysis of Nonlinear Models with Few Repeated Measurements, *Stat Med*, 26: 1901-1919 (2007).
- 161) D. Kim*, M. E. Andersen, Y.-C. E. Chao, P. P. Egeghy*, **S. M. Rappaport**, and L. A. Nylander-French, Human Dermal and Inhalation Exposures to Jet Fuel Can Be Predicted Using a PBTK Model, *Environ Health Perspect*, 115(6): 894-901 (2007).
- 162) S. Waidyanatha and **S. M. Rappaport**, Hemoglobin and Albumin Adducts of Naphthalene-1,2-oxide, 1,2-Naphthoquinone and 1,4-Naphthoquinone in Swiss Webster mice, *Chemico Biol Interact*, 172: 105-114 (2008).
- 163) Y.S. Lin, P.P. Egeghy, and **S. M. Rappaport**, Relationships Between Levels of Volatile Organic Compounds in Air and Blood from the General Population, *J Exposure Sci Environ Epidemiol*, 18(4): 421-429 (2008).
- 164) D. J. Taylor, L. L. Kupper, B. A. Johnson, S. Kim, and **S. M. Rappaport**, Parametric Methods for Evaluating Nonlinear Exposure-Biomarker Relationships when the Predictor and the Response Variables are Measured with Error, *J Agric Biol Environ Stat*, 13(4): 367-387 (2008).
- 165) S. Fustinoni, L. Campo, P. Manini, M. Buratti, S. Waidyanatha, G. De Palma, A. Mutti, V. Foa, A. Columbi, and **S.M. Rappaport**, *Biomarkers*, 13(6): 560-578 (2008).
- 166) W. E. Funk*, S. Waidyanatha, S. H. Chaing, and **S. M. Rappaport**, Hemoglobin Adducts of Benzene Oxide in Neonatal and Adult Dried Blood Spots, *Cancer Epidemiol Biomark Prevent*, 17(8):1896-901 (2008).
- 167) J. R. Sobus*, J. D. Pleil, M. C. Madden, W. E. Funk*, H. F. Hubbard, and **S.M. Rappaport**, Identification of Surrogate Measures of Diesel Exhaust Exposure in a Chamber Study with Human Subjects, *Environ Sci Technol*, 42(23):8822-8828 (2008).
- 168) J.R. Sobus*, S. Waidyanatha, M.D. McClean, R.F. Herrick, T.J. Smith, E. Garshick, F. Laden, J.E. Hart, Y. Zheng, and **S.M. Rappaport**, Urinary Naphthalene and Phenanthrene as Biomarkers of Occupational Exposure to Polycyclic Aromatic Hydrocarbons, *Occup Environ Med*, 66(2):99-104 (2009). Epub 2008 Nov 18
- 169) Q. Lan, L. Zhang, M. Shen, W. J. Jo, R. Vermeulen, G. Li, C. Vulpe, S. Lim, X. Ren, **S.M. Rappaport**, S. Berned, M. Yeager, J. Yuenger, R.B. Hayes, M. Linet, S. Yin, S. Chanock, M.T. Smith, and N. Rothman, Large-scale Evaluation of Candidate Genes Identifies Associations between DNA Repair and Genomic Maintenance and Development of Benzene Hematotoxicity, *Carcinogenesis*, 30(1):50-58 (2009). Epub 2008 Oct 31.

- 170) T. Whitehead*, C. Metayer, M.H. Ward, M.G. Nishioka, R. Gunier, J.S. Colt, P. Reynolds, S. Selvin, P. Buffler, and **S.M. Rappaport**. Is house-dust nicotine a good surrogate for household smoking? *Am J Epidemiol*, 169(9):1113-23 (2009). Epub 2009 Mar 18.
- 171) C. McHale, L. Zhang, Q. Lan, G. Li, A. E. Hubbard, M. S. Forrest, R. Vermeulen, J. Chen, M. Shen, **S.M. Rappaport**, S. Yin, M. T. Smith, N. Rothman, Changes in the Peripheral Blood Transcriptome Associated with Occupational Benzene Exposure Identified by Cross-Comparison on Two Microarray Platforms, *Genomics*, 93(4):343-349 (2009). Epub 2009 Jan 20.
- 172) F. Onyemauwa†, **S.M. Rappaport**, J. R. Sobus*, D. Gajdošová, R. Wu†, and Suramya Waidyanatha, Using Liquid Chromatography-Tandem Mass Spectrometry to Quantitate Monohydroxylated Metabolites of Polycyclic Aromatic Hydrocarbons in Urine, *J Chromatog B*, 877(11-12):1117-1125 (2009). Epub 2009 Mar 5.
- 173) **S. M. Rappaport** , S. Kim*, Q. Lan, R. Vermeulen, S. Waidyanatha, L. Zhang, G. Li, S. Yin, R. B. Hayes, M. T. Smith, and N. Rothman, Evidence that Humans Metabolize Benzene via Two Pathways, *Environ Health Perspect*, 117(6):946-952 (2009).
- 174) W.B. Allshouse, J.D. Pleil, **S. M. Rappaport**, and M.L. Serre. Mass Fraction Spatiotemporal Geostatistics and its Application to Map Atmospheric Polycyclic Aromatic Hydrocarbons after 9/11, *Stochastic Environmental Research & Risk Assessment*, 23: 1213-1223 (2009). doi:10.1007/s00477-009-0326-y
- 175) J.R. Sobus*, M.D. McClean, R.F. Herrick, S. Waidyanatha, F. Onyemauwa†, L.L. Kupper, and **S.M. Rappaport**, Investigation of PAH Biomarkers in the Urine of Workers Exposed to Hot Asphalt, *Ann Occup Hyg*, 53(6): 551-560 (2009).
- 176) J.R. Sobus*, M.D. McClean, R.F. Herrick, S. Waidyanatha, L. Nylander-French, L.L. Kupper, and **S.M. Rappaport**, Comparing Urinary Biomarkers of Airborne and Dermal Exposure to Polycyclic Aromatic Compounds in Asphalt-Exposed Workers, *Ann Occup Hyg*, 53(6): 561-571 (2009).
- 177) T. Whitehead*, R. B. Gunier, M. H. Ward, M. G. Nishioka, C. Metayer, P. Buffler, and **S.M. Rappaport**, Determinants of Polycyclic Aromatic Hydrocarbon Levels in House Dust, *J Exposure Sci Environ Epidemiol*, 169: 1113-1123 (2009).
- 178) S. Fustinoni, P. Manini, L. Campo, G. De Palma, R. Andreoli, A. Mutti, P. A. Bertazzi, and **S.M. Rappaport**, Assessing Variability and Comparing Short-term Biomarkers of Styrene Exposure Using a Repeated Measurements Approach, *Toxicol Lett*, 142(1): 40-44 (2010).
- 179) L. Zhang, X. Tang, N. Rothman, R. Vermeulen, Z. Ji, M. Shen, C. Qiu, W. Guo, S. Liu, B. Reiss, L. Beane-Freeman, Y. Ge, A.E. Hubbard, M. Hua, A. Blair, N. Galvan, X. Ruan, B.P. Alter, K.X. Xin, S. Li, L.E. Moore, S. Kim, Y. Xie, R.B. Hayes, M. Azuma, M. Hauptmann, J. Xiong, P. Stewart, L. Li, **S.M. Rappaport**, H. Huang, J.F. Fraumeni Jr., M.T. Smith, Q. Lan, Occupational Exposure to Formaldehyde, Hematotoxicity and Leukemia-specific Chromosome Changes in Cultured Myeloid Progenitor Cells, *Cancer Epidemiol Biomark Prevent*, 19(1):80-88 (2010).
- 180) W. E. Funk*, H. Li†, A. T. Iavarone, E. R. Williams, J. Riby, and **S.M. Rappaport**, Enrichment of Cysteinyl Adducts of Human Serum Albumin, *Analyt Biochem*, 400: 61-68 (2010).
- 181) M. K. Chung*, J. Riby, H. Li†, A. T. Iavarone, E. R. Williams, Y. Zheng, and **S.M. Rappaport**, A Sandwich ELISA for Adducts of Polycyclic Aromatic Hydrocarbons with Human Serum Albumin, *Analyt Biochem*, 400: 123-129 (2010).
- 182) **S.M. Rappaport**, S. Kim*, Q. Lan, G. Li, R. Vermeulen, S. Waidyanatha, L. Zhang, S. Yin, M. T. Smith, and N. Rothman, Human Benzene Metabolism Following Occupational and Environmental Exposures, *Chemico-Biol Interact*, 184: 189-195 (2010).
- 183) L. Zhang, C.M. McHale, N. Rothman, G. Li, Z. Ji, R. Vermeulen, A.E. Hubbard, X. Ren, M. Shen, **S.M. Rappaport**, M. North, C.F. Skibola, S. Yin, C. Vulpe, S.J. Chanock, M.T. Smith, and Q. Lan, Systems Biology of Human Benzene Exposure, *Chemico-Biol Interact*, 184: 86-93 (2010).
- 184) C. Xing, F. Marchetti, G. Li, R. H. Weldon , E. Kurtovich, S. Young, T. E. Schmid, L. Zhang, **S. M. Rappaport**, S. Waidyanatha, A. J. Wyrobek, B. Eskenazi, Benzene Exposure Near the US Permissible Limit Is Associated With Sperm Aneuploidy, *Environ Health Perspect*, 118: 833-839 (2010).
- 185) **S.M. Rappaport** and M. T. Smith, Environment and Disease Risks, *Science*, 330: 460-461 (2010).

- 186) J.R. Sobus, J. D. Pleil, M. D. McClean, R. F. Herrick, and **S.M. Rappaport**, Biomarker Variance Component Estimation for Exposure Surrogate Selection and Toxicokinetic Inference, *Toxicol Letters* 15;199(3): 247-53 (2010).
- 187) **S.M. Rappaport**, Implications of the Exposome for Exposure Science, *J Exposure Sci Environ Epidemiol*, 21: 5-9 (2011).
- 188) S. Liu*, S. K. Hammond, and **S.M. Rappaport**, Statistical Modeling to Determine Sources of Variability in Exposures to Welding Fumes, *Ann Occup Hyg*, 55(3):305-18 (2011).
- 189) M.T. Smith, L. Zhang, C.M. McHale, S. Skibola, and **S.M. Rappaport**, Benzene, Exposomics and Future Investigations of Leukemia Etiology, *Chemico Biol Interact*, 119(5):628-34 (2011).
- 190) H. Li†, H. Grigoryan†, W. E. Funk*, S. S. Lu*, S. Rose*, E. R. Williams, and **S.M. Rappaport**, Profiling Cys³⁴ Adducts of Human Serum Albumin by Fixed-Step Selected Reaction Monitoring, *Mol Cell Proteomics*, 10(3):M110.004606 (2011).
- 191) C.M. McHale, L. Zhang, Q. Lan, R. Vermeulen, G. Li, A.E. Hubbard, K.E. Porter, R. Thomas, C.J. Portier, M. Shen, **S.M. Rappaport**, S. Yin, M.T. Smith, and N. Rothman, Global Gene Expression Profiling of a Population Exposed to a Range of Benzene Levels, *Environ Health Perspect*, 119(5):628-34 (2011).
- 192) T. Whitehead*, C. Metayer, R.B. Gunier, M.G. Nishioka, P. Buffler, and **S.M. Rappaport**, Determinants of polycyclic aromatic hydrocarbon levels in house dust, *J Exposure Sci Environ Epidemiol*, 21(2): 123-132 (2011).
- 193) S. Johannesson*, **S.M. Rappaport**, G. Sallsten, Variability of Environmental Exposure to Fine Particles, Black Smoke and Trace Elements Among a Swedish Population, *J Exposure Sci Environ Epidemiol*, 21(5): 506-514 (2011).
- 194) T. Whitehead*, C. Metayer, P. Buffler, and **S.M. Rappaport**, Estimating Exposures to Indoor Contaminants using Residential Dust, *J Exposure Sci Environ Epidemiol*, 21(6): 549-564 (2011).
- 195) J. Vlaanderen, L. Portengen, **S.M. Rappaport**, H. Kromhout, and R. Vermeulen, The Impact of Saturable Metabolism on Exposure-Response Relations in Two Studies of Benzene Induced Leukemia, *Am J Epidemiol*, 174(5): 621-629 (2011).
- 196) J.C. Kang-Sickel, M.A. Butler, L. Frame, B. Serdar, Y.C. Chao, P. Egeghy, **S.M. Rappaport**, C. Toennis, W. Li, T. Borisova, J.E. French, L.A. Nylander-French, The Utility of Naphthyl-keratin Adducts as Biomarkers for Jet-fuel Exposure, *Biomarkers*, 16(7): 590-599 (2011)
- 197) L. Zhang, Q. Lan, W. Guo, A.E. Hubbard, G. Li, **S.M. Rappaport**, C.M. McHale, M. Shen, Z. Ji, R. Vermeulen, S. Yin, N. Rothman, M.T. Smith, Chromosome-wide Aneuploidy Study (CWAS) in Workers Exposed to an Established Leukemogen, Benzene, *Carcinogenesis*, 32(4): 605-612 (2011).
- 198) **S.M. Rappaport**, H. Li†, H. Grigoryan†, W.E. Funk, and E.R. Williams, Adductomics: Characterizing Exposures to Reactive Electrophiles, *Toxicol Letters*, 13;213(1):83-90 (2012). DOI:10.1016/j.
- 199) F. Marchetti, B. Eskenazi, R. H. Weldon, G. Li, L. Zhang, **S.M. Rappaport**, T. E. Schmid, C. Xing, E. Kurtovich and A. J. Wyrobek, Occupational Exposure to Benzene and Chromosomal Structural Aberrations in the Sperm of Chinese Men, *Environ Health Perspect*, 120(2):229-34, DOI: 10.1289/ehp.1103921.
- 200) **S. M. Rappaport**, Discovering Environmental Causes of Disease, *J Epidemiol Comm Health*, 66: 99-102 (2012). DOI:10.1136/jech-2011-200726.
- 201) T.P Whitehead*, J.R. Nuckols, M.H. Ward and **S.M. Rappaport**, Carpet-dust Chemicals as Measures of Exposure: Implications of Variability, *Emerg Themes Epidemiol*, 9(1):2 (2012) DOI: 10.1186/1742-7622-9-2.
- 202) H. Grigoryan†, H. Li†, A.T. Iavarone, E.R. Williams and **S.M. Rappaport**, Cys³⁴ Adducts of Reactive Oxygen Species in Human Serum Albumin, *Chem Res Toxicol*, 25(8):1633-42 (2012). DOI: 10.1021/tx300096a.
- 203) **S.M. Rappaport**, Biomarkers Intersect with the Exposome, *Biomarkers*, 17(6):483-9 (2012). DOI: 10.3109/1354750X.2012.691553.
- 204) L. Zhang, Q. Lan, Z. Ji, G. Li, M. Shen, R. Vermeulen, W. Guo, A.E. Hubbard, C.M. McHale, **S.M. Rappaport**, R.B. Hayes, M.S. Linet, S. Yin, M.T. Smith and N. Rothman, Leukemia-related Chromosomal Loss Detected in Hematopoietic Progenitor Cells of Benzene-exposed Workers, *Leukemia*, 26(12): 2494-2498 (2013). DOI: 10.1038/leu.2012.143.

- 205) **S.M. Rappaport**, S. Kim, R. Thomas, B.A. Johnson, F.Y. Bois and L.L. Kupper, Low-dose Metabolism of Benzene in Humans: Science and Obfuscation, *Carcinogenesis*, 34(1): 2-9 (2013). DOI: 10.1093/carcin/bgs382.
- 206) T.P. Whitehead†, C. Metayer, M. Petreas, M. Does, P.A. Buffler and **S.M. Rappaport**. Polycyclic Aromatic Hydrocarbons in Residential Dust: Sources of Variability, *Environ Health Perspect*, 121(5):543-50 (2013). DOI: 10.1289/ehp.1205821. Epub 2013 Mar 4.
- 207) M.K Chung*, L. Regazzoni, M. McClean, R. Herrick and **S.M. Rappaport** SM., A Sandwich ELISA for Measuring Benzo[a]pyrene-albumin Adducts in Human Plasma, *Anal Biochem*. Apr 15;435(2) :140-149 (2013). DOI: 10.1016/j.ab.2012.12.021. Epub 2013 Jan 16.
- 208) T.P. Whitehead†, M.H. Ward, J.S. Colt, M.G. Nishioka, P.A. Buffler, **S.M. Rappaport** and C. Metayer, Determinants of Polychlorinated Biphenyls in Dust from Homes in California, *Environ Sci Processes and Impacts*, (2013), DOI: 10.1039/c2em30721a.
- 209) T.P. Whitehead†, F.R. Brown, C. Metayer, J.S. Park, M. Does, M.X. Petreas, P.A. Buffler and **S.M. Rappaport**, Polybrominated Diphenyl Ethers in Residential Dust: Sources of Variability, *Environ Int.*, 57-58:11-24 (2013). doi: 10.1016/j.envint.2013.03.003. Epub 2013 Apr 27.
- 210) T.P. Whitehead†, C. Metayer, J.S. Park, M. Does, P.A. Buffler and **S.M. Rappaport**, Levels of Nicotine in Dust from Homes of Smokeless Tobacco Users, *Nicotine Tob Res*, 15(12):2045-52 (2013). doi: 10.1093/ntr/ntt096. Epub 2013 Jul 24. PMID: 23884321 PMID:24313682.
- 211) R. Thomas, C.M. McHale, Q. Lan, A.E. Hubbard, L. Zhang, R. Vermeulen, G. Li, **S.M. Rappaport**, S. Yin, N. Rothman and M.T. Smith, Global Gene Expression Response of a Population Exposed to Benzene: a Pilot Study Exploring the Use of RNA-sequencing Technology, *Environ Mol Mutagen*, 2013 Aug;54(7):566-73. doi: 10.1002/em.21801. Epub 2013 Aug 1.
- 212) M.K. Chung*, H. Grigoryan, A.T. Iavarone, **S.M. Rappaport**. Antibody Enrichment and Mass Spectrometry of Albumin-cys34 Adducts. *Chem Res Toxicol*. Dec 24. 2013 [Epub ahead of print] PMID:24328277
- 213) **S.M. Rappaport**, D. Barupal, D. Wishart, P. Vineis and A. Scalbert, The Blood Exposome and its Role in Discovering Causes of Disease, *Environ Health Perspect*, March 21, 2013 [Epub ahead of print]. PMID: 24659601

Books, Book Chapters and Published Proceedings:

- 1) **S.M. Rappaport**, S. Selvin, R.C. Spear and C. Keil, An Evaluation of Statistical Schemes for Air Sampling, in, Chemical Hazards in the Workplace Environment, G. Choudhary, ed., ACS Symposium Series, American Chemical Society, Washington, DC, pp. 431-453, 1981.
- 2) E. T. Zellers, R. M. White, **S.M. Rappaport**, and S. W. Wenzel, Selective Surface-Acoustic Wave Styrene Vapor Sensor with Regenerable Reagent Coating, Transducers '87, 1988, pp. 459-461.
- 3) S.F. Liu, **S.M. Rappaport**, K. Pongrascz, and W. Bodell, Detection of Styrene Oxide-DNA Adducts in Lymphocytes of a Worker Exposed to Styrene, in, Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention, H. Bartsch, K. Hemminki, and I.K. O'Neill, eds., IARC Scientific Publications No.89, Lyon, France, pp. 217-212, 1988.
- 4) **S.M. Rappaport**, Biological Considerations for Designing Sampling Strategies, in Advances in Air Sampling, W. John, ed., Lewis Publishers, Chelsea, Michigan, 1988, pp. 337-352.
- 5) J. W. Yager, J.W., W. Paradisn, E. Symanski and **S.M. Rappaport**, Sister-Chromatid Exchanges Induced in Peripheral Lymphocytes of Workers Exposed to Low Concentrations of Styrene, in, Mutation and the Environment - Part C: Somatic and Heritable Mutation, Adduction and Epidemiology., M. Mendelsohn and R. J. Albertini, eds., Wiley-Liss, New York, 1990, pp. 271-282.
- 6) W.J. Bodell, K. Pongrascz, S. Kaur, A.L. Burlingame, S.F. Liu, and **S.M. Rappaport**, Investigation of Styrene Oxide-DNA Adducts and their Detection in Workers Exposed to Styrene, in, Mutation and the Environment - Part C: Somatic and Heritable Mutation, Adduction and Epidemiology., M. Mendelsohn and R. J. Albertini, eds., Wiley-Liss, New York, 1990, pp. 347-356.

- 7) **S.M. Rappaport**, Exposure Assessment Strategies, in Exposure Assessment for Occupational Epidemiology and Hazard Control, S.M. Rappaport and T. Smith, eds., Lewis Publishers, Chelsea, Michigan, 1990, pp. 219-249.
- 8) **S.M. Rappaport** and T. Smith, eds., Exposure Assessment for Occupational Epidemiology and Hazard Control, Lewis Publishers, Chelsea, Michigan, 1990.
- 9) H. Checkoway, L.C. Costa, T. Coccini, **S.M. Rappaport** and L. Manzo, Monitoring Styrene Neurotoxicity with ³H-Spiperone Binding to Lymphocytes, Occupational Epidemiology, H. Sakurai et al., eds. Elsevier Science Publishers B.V., Amsterdam, 1990, pp. 197-200.
- 10) **S.M. Rappaport**, Interpreting Levels of Exposure to Chemical Agents, in Patty's Industrial Hygiene and Toxicology, 3-rd Edition, Part A, R. L. Harris, L. J. Cralley and L. V. Cralley, eds., John Wiley, New York, NY, 1994, pp. 349-403.
- 11) **S.M. Rappaport**, Interpreting Levels of Exposure to Chemical Agents, in Patty's Industrial Hygiene, 4th Edition, Part A, R. L. Harris, L. J. Cralley and L. V. Cralley, eds., John Wiley, New York, NY, 2000, pp. 679-745.
- 12) J. D. Pleil, D. Kim, J. D. Prah, D. L. Ashley, and **S.M. Rappaport**, The Unique Value of Breath Biomarkers for Estimating Pharmacokinetic Rate Constants and Body Burden from Environmental Exposure, in Breath Analysis For Clinical Diagnosis and Therapeutic Monitoring, A. Amann and D. Smith, eds., World Scientific Publishing Co. Pte. Ltd., 27, Hackensack, NJ, 2005, pp. 347-360.
- 13) **S.M. Rappaport** and L.L. Kupper, Quantitative Exposure Assessment. First ed. El Cerrito, CA: Stephen Rappaport, 2008; <http://www.lulu.com/content/1341905>.
- 14) **S.M. Rappaport** and L.L. Kupper, Some Implications of Random Exposure Measurement Errors in Occupational and Environmental Epidemiology. in Molecular Epidemiology of Chronic Diseases, C. Wild, P. Vineis, and S. Garte (eds.), John Wiley and Sons, Ltd., West Sussex, England, 2008, pp. 223-230
- 15) **S.M. Rappaport** and L.L. Kupper, Interpreting Levels of Exposure to Chemical Agents, in Patty's Industrial Hygiene and Toxicology, 6-th Edition, Vol. 2: Evaluation and Control, V. Rose and B. Cohrssen, eds., John Wiley, New York, NY, 2011, pp. 827-863.

Published Letters, Editorials and Workshop Summaries (since 1990):

- 1) **S.M. Rappaport**. Response to H. Kromhout and D. Heederik Re: "Assessment of Long-Term Exposures to Toxic Substances in Air, Reply," *Ann Occup Hyg*, 35:674 (1991).
- 2) **S.M. Rappaport** and S.A. Roach. Response to ACGIH Re: "But They Are Not Thresholds: A Critical Analysis of The Documentation of Threshold Limit Values," *Am J Ind Med*, 20:429-430 (1991).
- 3) **S.M. Rappaport**, E. Symanski, R. Lyles and H. Kromhout. Response to T.M.L. Scheffers, C.J. Cole and M.R. Gomez Re: Variation of Exposure Between Workers in Homogenous Exposure Groups," *Am Ind Hyg Assoc J*, 55:875-877 (1994).
- 4) **S.M. Rappaport** and J.W. Yager. Correspondence Re: Scott, D. and Preston, R.J. "A re-evaluation of the cytogenetic effects of styrene," *Mutat Res*, 318:175-203 (1994), *Mutat Res*, 340:183-185 (1996).
- 5) **S.M. Rappaport**, R. Tornero-Velez and P. Egeghy. Correspondence Re: Hewett, P. "Mean Testing: I Advantages and Disadvantages," *Appl Occup Environ Hyg*, 12:339-346 (1998) and Hewett, P. "Mean Testing: II Comparison of several alternative procedures," *Appl Occup Environ Hyg*, 12:339-346 (1998), *Appl Occup Environ Hyg*, 14:202-203 (1998).
- 6) **S.M. Rappaport**, R. Tornero-Velez, E. Symanski, H. Kromhout and R. C. Yu. Response to Paul Hewett Re: "Compliance Versus Risk in Assessing Occupational Exposures," *Risk Anal*, 18:669 (1998).
- 7) **S.M. Rappaport**, L. L. Kupper and R. H. Lyles. Response to Paul Hewett Re: "A Lognormal Distribution-Based Exposure Assessment Method for Unbalanced Data," *Ann Occup Hyg* 42:413-422 (1998).
- 8) **S.M. Rappaport** and M. Flynn. Commentary Re: "Two Seminal Contributions of S. A. Roach to the Evaluation and Control of Hazardous Substances in Air". *Ann Occup Hyg*, 47(5): 343-348 (2003).

- 9) **S. M. Rappaport** and R. Tornero-Velez. Correspondence Re: Csanady, G.A., *et al.* “A toxicokinetic model for styrene and its metabolite, styrene-7,8-oxide in mouse, rat and human with special emphasis on the lung,” *Toxicol Lett*, 138:75-102 (2003), *Toxicol Lett*, 144: 271-272 (2003).
- 10) M. Toraason, R. Albertini, S. Bayard, W. Bigbee, A. Blair, P. Boffetta, S. Bonassi, S. Chanock, D. Christiani, D. Eastmond, S. Hanash, C. Henry, F. Kadlubar, F. Mirer, D. Nebert, **S. M. Rappaport**, K. Rest, N. Rothman, A. Ruder, R. Savage, P. Schulte, J. Siemiatycki, P. Shields, M. Smith, P. Tolbert, R. Vermeulen, P. Vineis, S. Wacholder, E. Ward, M. Waters, and A. Weston. “Applying New Biotechnologies to the Study of Occupational Cancer – A Workshop Summary,” *Environ Health Perspect*, 112(4) 413-416 (2004).
- 11) L.S. Welch, **S.M. Rappaport** and P. Susi. “Construction Welding Exposures to Manganese Likely to Exceed Proposed TLV”, *J Occup Environ Hyg*, 1: D1-D3 (2004).
- 12) **S. M. Rappaport**, Y. S. Lin, and L. L. Kupper. Response to Hans Kromhout Re: “Air Samples versus Biomarkers for Epidemiology,” *Occup Environ Med* 62: 750-760 (2005). Letters published in *Occup Environ Med* Online, 23 Nov. 2005 and 6 Dec. 2005.
- 13) Q. Lan, R. Vermeulen, L. Ziang, G. Li, P.S. Rosenberg, B. P. Alter, M. Shen, **S. M. Rappaport**, R.S. Weinberg, S. Channock, S. Waidyanatha, C. Rabkin, R.B. Hayes, M. Linet, S. Kim, S. Yin, N. Rothman, M.T. Smith. Response to S. Lamm and H. W. Grunwald Re: “Hematotoxicity in Workers Exposed to Low Levels of Benzene,” *Science*, 306: 1776-1776 (2004). Letters published in *Science*, 312: 998-999 (2006).
- 14) M. T. Smith and **S.M. Rappaport**, “Building Exposure Biology Centers to Put the E into GxE Interaction Studies”. Editorial in *Environ Health Perspect*, 117(8): A334-A335 (2009).
- 15) **S.M. Rappaport**, “Assessing Workplace Exposures – Turning to the Past for Guidance”. Editorial in *Occup Environ Med*, 66(7): 429-430 (2009).
- 16) E.B. Bookman, K. McAllister, E. Gillanders, K. Wanke, D. Balshaw, J. Rutter, J. Reedy, D. Shaughnessy, T. Agurs-Collins, D. Paltoo, A. Atienza, L. Bierut, P. Kraft, M.D. Fallin, F. Perera, E. Turkheimer, J. Boardman, M.L. Marazita, **S.M. Rappaport**, E. Boerwinkle, S.J. Suomi, N.E. Caporaso, I. Hertz-Picciotto, K.C. Jacobson, W.L. Lowe, L.R. Goldman, P. Duggal, M.R. Gunnar, T.A. Manolio, E.D. Green, D.H. Olster, and L.S. Birnbaum. “Gene-environment Interplay in Common Complex Diseases: Forging an Integrative Model - Recommendations from an NIH Workshop,” *Genet Epidemiol*. 2011 Feb 9. doi: 10.1002/gepi.20571.
- 17) P. Lioy and **S.M. Rappaport**, Exposure Science and the Exposome: An Opportunity for Coherence in the Environmental Health Sciences, Editorial, *Environ Health Perspect*, 119(11): A466-A467 (2011).
- 18) **S.M. Rappaport**, B.A. Johnson, F.Y. Bois, L.L. Kupper, S. Kim and R. Thomas, Ignoring and Adding Errors do not Improve the Science, letter to the editor, *Carcinogenesis*, 34(7): 1689-1691 (2013).

Invited Papers, Lectures and Seminars (since 1990):

- 1) *The Impact of Exposure Variability on Dose-Response Relationships*, Institute of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH, 31 January, 1990.
- 2) *Cysteinyl Adducts in Blood Proteins, Symposium on the Application of Molecular Biomarkers in Epidemiology*, National Institute for Environmental Health Sciences, Research Triangle Park, NC, 21-22 February 1990.
- 3) *Selection of the Measures of Exposure for Epidemiology Studies*, International Workshop on Retrospective Exposure Assessment for Occupational Epidemiologic Studies, Leesburg, VA, 27-30 March 1990.
- 4) *Strategic Implications of Assessing Chemical Exposures*, Symposium on Air Sampling in the Chemical Industry, American Chemical Society annual meeting, Boston, MA, 23 April 1990.
- 5) *General Principles of Exposure Assessment*, NCI-NIOSH Workshop on the Use of biologic Markers in occupational epidemiologic investigations of cancer, Williamsburg, VA, 1-2 May 1990.
- 6) *Some Implications of OSHA's Use of the TLVs in its Air Contaminants Standard*, Industrial Hygiene Program, Corporate Headquarters, Chevron Oil Company, San Francisco, CA, 5 June 1990.
- 7) *Exposure Assessment Strategies*, Ontario Ministry of Labour, Health and Safety Regulations Unit, Toronto, Canada, 27-28 August 1990.
- 8) *Selection of the Measure of Exposure*, Second Seminar and Workshop on Exposure Assessment: On the Concepts of Occupational Exposure Assessment, Sigtuna, Sweden, 6-7 September 1990.

- 9) *Critical Review of the ACGIH TLVs*, Professional Conference on Industrial Hygiene, Vancouver, British Columbia, Canada, 24 October 1990.
- 10) *Selection of Measures of Exposure for Epidemiology Studies*, Environmental Biostatistics Seminar Series, Dept. of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, N.C., February 1991.
- 11) *TLVs, PELs and Significant Risk*, Wisconsin Section of the American Industrial Hygiene Association, Pewaukee, WI, 9 April 1991.
- 12) *Strategies for Assessing Long-Term Exposures to Toxic Substances*, 49th Wisconsin Safety and Health Congress, Oconomowoc, WI, 10 April 1991.
- 13) *Discrepancies Among Threshold Limit Values*, 1992 Mobil Workplace Health Protection Technical Seminar, San Diego, California, 26 February 1992.
- 14) *Selection of Quantitative Measures of Exposure for Dose-Response Relationships*, Workshop on Exposure Assessment, Institute for Occupational Medicine, Edinburgh, Scotland, 13-14 April, 1992.
- 15) *Assessment of Exposure between Workers in Homogeneous Groups*, 1992 American Industrial Hygiene Conference, Boston, MA., 30 May - 5 June, 1992.
- 16) *Biological Considerations in Assessing Exposures to Mutagenic and Carcinogenic Agents* (keynote lecture), First International Symposium on Biological Monitoring, Kyoto, Japan, 12-15 October 1992.
- 17) *The Bases of Occupational Exposure Limits in the U.S.A.*, First International Scientific Conference of the International Occupational Hygiene Association, Brussels, Belgium, 7-9 December 1992.
- 18) *Assessing Variable Exposures Relative to Limits*, Workshop on Occupational Exposure Assessment: Investigating Why Concentration Measurements Vary, First International Scientific Conference of the International Occupational Hygiene Association, Brussels, Belgium, 10 December 1992.
- 19) *Relationship between Environmental Monitoring and Biological Markers for Exposure Assessment*, National Human Tissue Monitoring and Specimen Banking: Opportunities for Exposure Assessment, Risk Assessment and Epidemiologic Research, Research Triangle Park, NC, 30-31 March 1993.
- 20) *Why Exposure Limits are Like Sausages*, Air, Radiation and Industrial Hygiene Program, University of North Carolina, Dept. of Environmental Sciences and Engineering, Chapel Hill, NC, March 1993.
- 21) *Exposure Variability, Homogeneous-Exposure Groups, and Exposure Assessment*, Department of Industrial Medicine, University of Linköping, Linköping, Sweden, 1 September 1993.
- 22) *Exposure Variability, Homogeneous-Exposure Groups, and Exposure Assessment*, Department of Internal Medicine, University of Gothenburg, Gothenburg, Sweden, 3 September 1993.
- 23) *Investigations of Exposure Variability and Exposure-Biomarker Relationships*, Epidemiology Branch, National Institute for Environmental Health Sciences, Research Triangle Park, NC, 27 September 1993.
- 24) *Investigations of Exposure Variability and Exposure-Biomarker Relationships*, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH, 15 October 1993.
- 25) *A Comparison of Environmental and Biological Monitoring for Styrene*, Division of Occupational and Environmental Medicine, Duke University Medical Center, Durham, NC, 19 October 1993.
- 26) *Principles of Exposure Assessment*, Guidelines for Exposure Assessment in Construction, Center to Protect Workers' Rights, Washington, D.C., 9 November 1993.
- 27) *Investigations of Exposure Variability and Exposure-Biomarker Relationships*, Department of Environmental Health and Community Medicine, University of Washington, Seattle, WA, 9 December 1993.
- 28) *The Relationship between Environmental Monitoring and Biological Markers in Exposure Assessment*, Occupational and Environmental Health Program, University of North Carolina School of Public Health, Chapel Hill, NC, 31 January 1994.
- 29) *Why Homogeneous Exposure Groups Aren't*, Air, Radiation and Industrial Hygiene Program, University of North Carolina, Dept. of Environmental Sciences and Engineering, Chapel Hill, NC, 1 February 1994.
- 30) *Exposure Biomarker Relationships for Styrene*, Departments of Epidemiology and Air Quality, Wageningen Agricultural University, Wageningen, The Netherlands, 3 March 1994.

- 31) *Air Sampling vs. Biomarkers for Assessing Exposures to Styrene*, Conference on Retrospective Assessment of Occupational Exposures in Epidemiology, International Agency for Research on Cancer, Lyon, France, 13 April 1994.
- 32) *Biological Monitoring and Standard Setting in the USA: A Critical Appraisal*, International Symposium on Human Health and Environment: Mechanisms of Toxicity and Biomarkers to Assess Adverse Affects of Chemicals, Salsomaggiore Terme, Italy, 25-30 September 1994.
- 33) *Relationship between Biomarkers and Traditional Exposure-Assessment Methods*, International Workshop on Methodological Issues in the Validation and Application of Biomarkers to Cancer Epidemiology Studies, Salsomaggiore Terme, Italy, 28 September 1994.
- 34) *Air Sampling versus Biological Monitoring for Assessing Exposure to Chemicals*, Institute for Occupational Medicine, University of Milan, Milan, Italy, 3 October 1994.
- 35) *Biomarkers of Exposure*, Departments of Epidemiology and Air Quality, Wageningen Agricultural University, Wageningen, The Netherlands, 3 November 1994.
- 36) *Biomarkers of Exposure Versus Environmental Measurements for Use in Epidemiology*, Occupational Epidemiology Unit (170) of INSERM, Paris, France, 7 November 1994.
- 37) *Investigations of Exposure Variability and Exposure-Biomarker Relationships*, Program in Occupational and Environmental Health, University of British Columbia, Vancouver, British Columbia, Canada, 9 December 1994.
- 38) *An Exposure-Assessment Strategy Accounting for Within- and Between-Worker Sources of Variability*, School of Public Health, University of California, Berkeley, California, 12 December 1994.
- 39) *Investigations of Exposure Variability and Exposure-Biomarker Relationships*, School of Public Health, University of Michigan, Ann Arbor, Michigan, 10 February 1995.
- 40) *Biomarkers of Styrene*, National Urban Air Toxics Center, University of Texas, Health Sciences Center, Houston, Texas, 28 April 1995.
- 41) *The Scientific Basis for Industrial-Hygiene Practice*, 1995 American Industrial Hygiene Conference, Kansas City, Missouri, 23 May 1995.
- 42) *Using Between-Worker Variation to Evaluate and Control Exposures*, 1995 American Industrial Hygiene Conference, Kansas City, Missouri, 25 May 1995.
- 43) *Biological Markers of Exposure and Dose*, Advanced Course in Occupational and Environmental Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands, 7 July 1995.
- 44) *Biomarkers of Exposure*, Advanced Course in Occupational and Environmental Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands, 10 July 1995.
- 45) *Development of an Exposure-Assessment Protocol*, Workshop on Theoretical and Practical Approaches to Exposure Assessment, sponsored by the Nickel Producers Environmental Research Association, Research Triangle Park, North Carolina, 7-8 November, 1995.
- 46) *Sampling Strategies for Exposure Assessment* (keynote lecture), Exposure Strategies and Methodology, Israeli Association of Occupational Hygiene, Tel Aviv, Israel, 5 February 1996.
- 47) *Sampling Strategies for Exposure Assessment*, Norwegian Institute for Occupational Health, Oslo, Norway, 6 March 1996.
- 48) *Biomarkers of Exposure and Dose*, Advanced Course in Occupational and Environmental Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands, 21 June 1996.
- 49) *Biomarkers of Exposure*, Advanced Course in Occupational and Environmental Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands, 21 June 1996.
- 50) *An Investigation of Molecular Dose Among Workers Exposed to Styrene and Styrene-7,8-Oxide: A Case for Biochemical Toxicology*, Department of Environmental Health and Physiology, Harvard University, School of Public Health, Boston, MA, 10 October 1996.
- 51) *An Investigation of Molecular Dose Among Workers Exposed to Styrene and Styrene-7,8-Oxide: A Case for Biochemical Toxicology*, Department of Epidemiology, University of North Carolina, School of Public Health, Chapel Hill, NC, 21 November 1996.

- 52) *Biomarkers of Exposure and their Use in Dose Response Assessment*, American Industrial Health Council and US EPA Symposium, Incorporating Human Data in Quantitative Risk Assessment for Carcinogens: Issues, Status, and Future Needs, New Orleans, LA, 10 December 1996.
- 53) *Hemoglobin and Albumin Adducts As Dosimeters for Human Exposure to Styrene and Benzene*, Genotoxicity and Environmental Mutagen Society Spring Symposium, North Carolina Biotechnology Center, Research Triangle Park, NC, 17 May, 1997.
- 54) *Protein Adducts as Dosimeters of Human Exposure to Styrene and Benzene*, Department of Occupational and Environmental Medicine, University of Umeå, Umeå, Sweden, 24 June 1997.
- 55) *Sources of Variability in Human Exposure: Applications to Hot Processes in the Construction Industry*, National Institute for Working Life, Umeå, Sweden, 17 June 1997.
- 56) *Protein Adducts as Dosimeters of Human Exposure to Styrene and Benzene*, Department of Chemistry, University of Newcastle, Newcastle, U.K., 1 July 1997.
- 57) *Use of ANOVA Models to Characterize Exposures of Occupational Groups*, Annual meeting of the International Society for Exposure Analysis, Research Triangle Park, NC, 2-5 November 1997.
- 58) *Roles for Biomarkers in Assessing Human Risks*, Annual meeting of the International Society for Exposure Analysis, Research Triangle Park, NC, 2-5 November 1997.
- 59) *Introduction to Occupational and Environmental Toxicology*, First International Course of Occupational and Environmental Epidemiology, Salvador, Brazil, 9-18 December 1997.
- 60) *Statistical Models for Exposure Assessment*, First International Course of Occupational and Environmental Epidemiology, Salvador, Brazil, 9-18 December 1997.
- 61) *Biological Markers of Exposure*, First International Course of Occupational and Environmental Epidemiology, Salvador, Brazil, 9-18 December 1997.
- 62) *Exposure Measurement Errors*, First International Course of Occupational and Environmental Epidemiology, Salvador, Brazil, 9-18 December 1997.
- 63) *Environmental Versus Biological Monitoring*, First International Course of Occupational and Environmental Epidemiology, Salvador, Brazil, 9-18 December 1997.
- 64) *Measurement of Occupational and Environmental Exposures*, First International Course of Occupational and Environmental Epidemiology, Salvador, Brazil, 9-18 December 1997.
- 65) *Exposure-Biomarker Relationships*, First International Course of Occupational and Environmental Epidemiology, Salvador, Brazil, 9-18 December 1997.
- 66) *Evolving Models of Occupational Exposure*, International Symposium on Industrial Hygiene, Taichung, Taiwan, April 1998.
- 67) *A Comparison Between Biomarkers and Traditional Exposure Assessment Methods for Use in Epidemiology*, International Symposium on Industrial Hygiene, Taichung, Taiwan, April 1998.
- 68) *Biomarkers of Exposure*, Advanced Course in Occupational and Environmental Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands, 15 June 1998.
- 69) *Biomarkers of Exposure and Dose*, Advanced Course in Occupational and Environmental Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands, 15 June 1998.
- 70) *Evolution of Strategies for Exposure Assessment* (keynote address), Dutch Occupational Hygiene Association and Contact Group in Chemistry, Utrecht, the Netherlands, 16 June 1998.
- 71) *Protein Adducts As Dosimeters of Human Exposure to Styrene and Benzene*, International Congress of Toxicology, Paris, France, 5-9 July, 1998.
- 72) *Protein Adducts as Dosimeters of Human Exposure to Styrene, Styrene-7,8-oxide and Benzene*, 4-th International Symposium on Biological Monitoring in Occupational and Environmental Health, Seoul, Korea, 23-25 September 1998.
- 73) *Biological Considerations in Assessing Exposure to Genotoxic and Carcinogenic Agents*, First International Course on Biomarkers: New Developments, Oslo, Norway, 2-6 November 1998.
- 74) *Assessment of Exposure in Epidemiological Studies*, First International Course on Biomarkers: New Developments, Oslo, Norway, 2-6 November 1998.
- 75) *The Evolution of Strategies for Exposure Assessment*, Third International Symposium on Modern Principles of Air Monitoring, Geilo, Norway, 10-14 February 1999.

- 76) *Biomarkers of Exposure*, Advanced Course in Occupational and Environmental Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands, 23 June 1999.
- 77) *Biomarkers of Exposure and Dose*, Advanced Course in Occupational and Environmental Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands, 23 June 1999.
- 78) *Principles of Exposure Assessment*, Department of Occupational Medicine, Odense University, Odense, Denmark, 2 February 2000.
- 79) *Exposure and Dose of Styrene and Styrene-7,8-oxide in Humans*, Department of Occupational Medicine, Odense University, Odense, Denmark, 2 February 2000.
- 80) *Evolving Strategies for Exposure Assessment*, Danish Society of Occupational Epidemiology, Odense, Denmark, 2 February 2000.
- 81) *Comparison of Self and Expert Assessment of Occupational Exposure by Applying Mixed Models*, Workshop on Chemical Exposure Assessment and Exposure Data Handling in Small and Medium Size Enterprises, Brussels, Belgium, 10 – 12 April 2000.
- 82) *Self Measurement of Benzene in Air and Breath during Gasoline Refueling*, Workshop on Chemical Exposure Assessment and Exposure Data Handling in Small and Medium Size Enterprises, Brussels, Belgium, 10–12 April 2000.
- 83) *The Use of Protein Adducts to Study the Metabolism of Styrene and Benzene*, 13th International Symposium on Microsomes and Drug Oxidations, Stresa, Italy, 10-14 July 2000.
- 84) *Self Measurement of Benzene in Air and Breath during Gasoline Refueling*, Institute for Occupational Medicine, University of Milan, Milan, Italy, 19 July 2000.
- 85) *Biomarkers for Exposure Assessment, Molecular Epidemiology Short Course*, Annual Meeting of the Environmental Mutagen Society, San Diego, CA, 15-16 March 2001.
- 86) *Increasing Sample Sizes for Exposure Assessment – A Critical Need for Occupational Hygiene* (keynote address), 10th Symposium of the Dutch Occupational Hygiene Society, Rotterdam, The Netherlands, 29 March 2001.
- 87) *Strategies for Assessing Exposures Relative to Occupational Exposure Limits (OELs)*, 10th Symposium of the Dutch Occupational Hygiene Society, Rotterdam, The Netherlands, 29 March 2001.
- 88) *Strategies for Assessing Exposures to Nickel Containing Substances*, NiPERA Workshop on Occupational Exposure and Health Assessment Guidelines for Nickel Operations, London, U.K., 3-4 April 2001.
- 89) *Comparing Environmental Measurements with Biomarkers of Exposure*, Symposium on Exposure Assessment for Controlling Chemical Risks, Beijing, China, 26-28 April 2001.
- 90) *Pharmacokinetic Adjustments of OELs for Unusual Work Schedules*, presented to the Environmental Affairs Committee, International Committee for Metals and the Environment (ICME), Montreal, Canada, 14 May 2001.
- 91) *Some Investigations Employing Biomarkers of Exposure to Benzene*, Department of Radiobiology, Stockholm University, Stockholm, Sweden, 15 June, 2001.
- 92) *Biomarkers of Exposure*, Advanced Course in Occupational and Environmental Epidemiology, Utrecht University, Utrecht, The Netherlands, 4 July 2001.
- 93) *Environmental Measurements versus Biomarkers of Exposure*, Advanced Course in Occupational and Environmental Epidemiology, Utrecht University, Utrecht, The Netherlands, 4 July 2001.
- 94) *Exposure Assessment In The Working Environment: State Of The Art And Future Trends*, National Institute for Working Life, Copenhagen, Denmark, 9 August, 2001.
- 95) *Mixed Models for Exposure Assessment: Relating Exposure Limits and Controls*, Exposure Assessment Strategies Symposium, Tampa, FL, 6 October, 2001.
- 96) *Saturable Metabolism of Benzene in Humans (A Successful Application Of Molecular Epidemiology?)*, Division of Environmental Health, School of Public Health, University of California, Berkeley, CA, 7 December, 2001.
- 97) *Human Metabolism of Benzene Based Upon Measurement of Protein Adducts*, Toxicokinetic Susceptibility Research Core, NIEHS Center for Environmental Susceptibility, University of North Carolina, Chapel Hill, 31 January 2002.

- 98) *Biomarkers of Exposure*, Advanced Course in Occupational and Environmental Epidemiology, Utrecht University, Utrecht, The Netherlands, 5 June 2002.
- 99) *Environmental Measurements versus Biomarkers of Exposure*, Advanced Course in Occupational and Environmental Epidemiology, Utrecht University, Utrecht, The Netherlands, 5 June 2002.
- 100) *Repeated Personal Monitoring Versus Microenvironmental Monitoring for Assessing Exposures to Airborne Chemicals*, 12th Conference of the International Society of Exposure Analysis, Vancouver. British Columbia, 11-15 August 2002.
- 101) *Assessing Exposures to Chemicals with Air and Biological Samples*, Dept. Environmental Sciences & Engineering, School of Public Health, University of North Carolina, Chapel Hill, NC, 23 October 2002.
- 102) *Using Biomarkers to Assess Exposures to Carcinogens*, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, 31 July, 2003.
- 103) *Evaluation of Exposures for Environmental Exposure Assessment*, keynote lecture, Second International Conference on Environmental, Health and Safety Aspects Related to the Production of Aluminium (EHASARPA 2003), St. Petersburg, Russia, 26 September – 1 October 2003.
- 104) *Naphthalene and Its Biomarkers as Measures of PAH Exposure*, Second International Conference on Environmental, Health and Safety Aspects Related to the Production of Aluminium (EHASARPA 2003), St. Petersburg, Russia, 26 September – 1 October 2003.
- 105) *Assessing Occupational Exposures to Chemicals*, Exposure Assessment Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV, November 13, 2003.
- 106) *Strategies to Assess Occupational Exposure to Cobalt Compounds in the Presence and Absence of Mixed Metal Exposure*, The Cobalt Development Institute Occupational Exposure Workshop, Chapel Hill, NC, 30-31 March, 2004.
- 107) *Statistical vs. Non-statistical Approaches for Exposure Assessment*, NIVA Course on Modern Statistical Methods in Exposure Assessment and its Implications for Research and Practice, Edsasdalen, Undersaker, Sweden, 18-23 April, 2004.
- 108) *Variability in Chemical Exposure*, NIVA Course on Modern Statistical Methods in Exposure Assessment and its Implications for Research and Practice, Edsasdalen, Undersaker, Sweden, 18-23 April, 2004.
- 109) *Exposure Variability and its Consequences for Practice: Maximum Allowable Concentrations, Measurement Strategy and Control Strategies*, NIVA Course on Modern Statistical Methods in Exposure Assessment and its Implications for Research and Practice, Edsasdalen, Undersaker, Sweden, 18-23 April, 2004.
- 110) *Protein Adducts as Measures of Bioactivation of Toxic Chemicals*, Seminar presented to the Chemistry Department, Wake Forest University, NC, 4 May, 2004.
- 111) *Statistical Methods for Evaluating Exposure-Biomarker Relationships*, (poster) presented at the annual meeting of the American Chemistry Council, Miami, Florida, 5-6 May, 2004.
- 112) *On the Importance of Cumulative Exposure to the Doses of Volatile Organic Compounds*, presented at XPASS 2004 (International Symposium on Exposure Assessment), Utrecht, the Netherlands, June 16, 2004.
- 113) *Dose vs. Dose Rate in Assessing Chemical Exposures - Are 'peaks' important?*, Center for Occupational and Environmental Health, University of Manchester, Manchester, U.K., 25 June 2004.
- 114) *A Measurement-Based Strategy Linking Exposure Assessment With Control*, presented to the Health and Safety Executive, Bootle, U.K., 28 June 2004.
- 115) *PAH Levels in Air Following the World Trade Center Disaster*, Dept. of Environmental Science and Technology, Imperial College, London, U.K., 30 June 2004.
- 116) *Biomarkers in Epidemiology*, Course on Epidemiology for Toxicologists, Institute for Risk Assessment Science, Utrecht University, Utrecht, The Netherlands, 26 August 2004.
- 117) *Protein Adducts as Biomarkers of Human Benzene Metabolism*, Recent Advances in Benzene Toxicity, Munich, Germany, 9-12 Oct. 2004.
- 118) *Relating Environmental Exposures to Health Effects*, presented to the Indoor Environment Department, Environmental Energy Technologies Division, Lawrence Berkeley National Laboratory, Berkeley, CA, 26 Jan. 2005.

- 119) *Dose-Response Modeling for Benzene*, Workshop on Representations of Dose-Response Relationships for Chemicals Associated with Non-Cancer Effects and their Policy Implications, Oakland, CA, 27-28 Jan. 2005.
- 120) *Relating Human Benzene Exposure to Internal Dose using PBPK Models and Biomarkers*, seminar presented to the Department of Biochemical and Molecular Toxicology, North Carolina State University, Raleigh, NC, 15 Feb. 2005.
- 121) *A Measurement-Based Strategy Linking Exposure Assessment With Control*, presented at the British Occupational Hygiene Conference, Manchester, U.K., 19 April 2005.
- 122) *The Impact of Exposure Peaks upon the Long-term Doses of Benzene Metabolites*, presented at the British Occupational Hygiene Conference, Manchester, U.K., 20 April 2005.
- 123) *World Trade Center: Study of the Levels and Composition of Polycyclic Aromatic Hydrocarbons Following the Disaster*, North Carolina Department of Environment and Natural Resources, Raleigh, NC, 1 June 2005.
- 124) *Differentiating Between Fire And Diesel Sources of Airborne Polycyclic Aromatic Hydrocarbons*, The Fifth International Symposium on Modern Principles of Air Monitoring, Loen, Norway, 12-16 June 2005.
- 125) *Air Sampling Versus Biomarkers for Assessing Chemical Exposures*, The Fifth International Symposium on Modern Principles of Air Monitoring, Loen, Norway, 12-16 June 2005.
- 126) *Recent Applications of PBPK Models to Determine the Impact of Exposure Variability (Peak Exposures) on the Long Term Doses of VOCs (Benzene, Perchloroethylene, Acetonitrile) and Their Metabolites*, First International Course on Peak Exposure and Human Health, Loen, Norway, 16-19 June 2005.
- 127) *Variability of Exposures of Construction Workers*, Center to Protect Workers' Rights, Silver Spring, MD, 27 July, 2005.
- 128) *An Overview of Statistical Approaches to Assessing Chemical Exposures*, American Statistical Association Annual Meeting, Minneapolis, MN, 10 August, 2005.
- 129) *Using Biomarkers to Define the Human Metabolism of Benzene*, School of Public Health, University of California, Berkeley, CA, 12 September 2005.
- 130) *Air Samples versus Biomarkers for Epidemiology*, Epidemiology Branch, National Institute for Environmental Health Sciences, Research Triangle Park, NC, 21 November 2005.
- 131) *Using Biomarkers to Define Human Benzene Metabolism*, Annual Science Retreat, Division of Extramural Research and Training, National Institute for Occupational Health, Wilmington, NC, 1 Dec. 2005.
- 132) *Are biomarkers better measures of exposure than air samples for epidemiology studies?*, Symposium of the U.K. Molecular Epidemiology Group, Imperial College London, U.K., 8 Dec. 2005.
- 133) *Are biomarkers better measures of exposure than air samples for epidemiology studies?*, Bilateral French-American Workshop on Biomarkers, Office of Science and Technology, Embassy of France in the United States, Charleston, SC, 17 Jan. 2006.
- 134) *Dose-related Metabolism of Benzene As Determined with Human Biomarkers*, Laboratory of Pharmacology & Chemistry, National Institute of Environmental Health Sciences, Research Triangle Park, NC, 26 Jan. 2006.
- 135) *Air Samples versus Biomarkers for Epidemiology*, U.S. Environmental Protection Agency, HEASD, Research Triangle Park, NC, 1 March 2006.
- 136) *Human Metabolism of Benzene As Determined with Urinary Biomarkers*, Cancer Epidemiology Group, University of California, School of Public Health, Berkeley, CA, 14 Aug. 2006.
- 137) *Collecting Exposure Data*, NIVA Course on Modern Statistical Methods in Exposure Assessment and Its Implications for Research and Practice 25-29, Åre, Sweden, 25-29 Sept. 2006.
- 138) *Exposure Distributions*, NIVA Course on Modern Statistical Methods in Exposure Assessment and Its Implications for Research and Practice 25-29, Åre, Sweden, 25-29 Sept. 2006.
- 139) *Mixed Models of Exposure*, NIVA Course on Modern Statistical Methods in Exposure Assessment and Its Implications for Research and Practice 25-29, Åre, Sweden, 25-29 Sept. 2006.
- 140) *Effects of Exposure-Measurement Errors in Estimating Human Risks*, NIVA Course on Modern Statistical Methods in Exposure Assessment and Its Implications for Research and Practice 25-29, Åre, Sweden, 25-29 Sept. 2006.

- 141) *Using Environmental Measurements and Biomarkers to Investigate Human Metabolism of Benzene*, 2006 National Environmental Health Conference 2006, Centers for Disease Control, Atlanta, GA, 4-6 Dec. 2006.
- 142) *Measuring Protein Adducts in Dried Blood Spots*, The Use of Newborn Blood Spots in Environmental Research: Opportunities and Challenges, University of North Carolina, Chapel Hill, NC, 20 Feb. 2007.
- 143) *Applying Biomarkers of Exposure to Benzene*, Annual Research Symposium, School of Public Health, University of California, Berkeley, 8 Mar. 2007.
- 144) *Opportunities for Improved Exposure Assessment Using Biomarkers from Dried Blood Spots*, Brain Tumor Epidemiology Consortium, Annual Meeting, Berkeley, California, 8 June, 2007.
- 145) *Low-level Exposures to Benzene are Converted to Toxic Metabolites Much More Efficiently than High-level Exposures*, International Congress of Toxicology, Montreal, Canada, 18 July, 2007.
- 146) *Benzene is Metabolized to Toxic Metabolites Much More Efficiently At Air Concentrations below 1 ppm*, ECNIS Advanced Course "A Critical Review of Environmental Mutagenesis and Carcinogenesis," Basel, Switzerland, 9 Sept. 2007.
- 147) *Using Biomarkers to Characterize Human Benzene Metabolism*, Public Health Applications of Human Biomonitoring, U.S. Environmental Protection Agency, 24 Sept. 2007.
- 148) *Complementary Roles for Environmental and Biological Monitoring in Epidemiology as Illustrated by Studies of Benzene Metabolism*, Keynote Address, The 19th International Conference on Epidemiology in Occupational Health, Banff, Alberta, Canada, 11 Oct. 2007.
- 149) *Exposure Assessment Strategies: the Academic's Perspective*. NIOSH Workshop on Exposure Sampling Strategies, Washington, D.C., 7 Nov. 2007.
- 150) *Air Samples versus Biomarkers for Epidemiology*. Environmental Health Sciences and Epidemiology Seminar, School of Public Health, University of California, Berkeley, CA, 8 April 2008.
- 151) *Using Environmental and Biological Monitoring to Elucidate Human Metabolism of Benzene*, Dept. of Environmental Radiation and Health Sciences, Colorado State University, Fort Collins, CO, 2 Oct. 2008.
- 152) *Strategies for Assessing Occupational Exposure: an Academic Perspective*, Dept. of Environmental Radiation and Health Sciences, Colorado State University, Fort Collins, CO 2 Oct. 2008.
- 153) *Hemoglobin Adducts in Dried Blood Spots as Measures of Carcinogen Exposures*, ISEE-ISEA Joint Annual Conference: Exposure and Health in a Global Environment, Pasadena, CA, 15 Oct. 2008.
- 154) *Issues Motivating the Collection of Occupational Exposure Data*, Workshop on Direct-Reading Exposure Assessment Methods, National Institute for Occupational Safety and Health, Washington, D.C., 13 Nov. 2008.
- 155) *Using Environmental Measurements and Biomarkers to Investigate Metabolism of Benzene*, Distinguished Lecturer Series, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, 10 Dec. 2008.
- 156) *Protein Adducts as Biomarkers of Exposure: Possibilities for the Future*, Distinguished Lecturer Series, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, 10 Dec. 2008.
- 157) *Using Environmental Measurements and Biomarkers to Investigate Metabolism of Benzene*, Division of Environmental Health, Department of Preventive Medicine, University of Southern California, Los Angeles, CA, 6 Feb., 2009.
- 158) *Implications of the Exposome for Exposure Assessment*, Connecting Innovations in Biological, Exposure and Risk Sciences: Better Information for Better Decisions, workshop sponsored by the International Council of Chemical Associations, Charleston, SC, 16-17 June 2009.
- 159) *Contributions of Occupational Hygiene to Exposure Science*, National Research Council Workshop on Exposure Science in the 21st Century, National Academy of Sciences, Washington, DC, 18-19 June 2009.
- 160) *Household Dust and Dried Blood Spots are Valuable Sources of Exposure Data*, keynote address, Annual Meeting of the Childhood Leukemia International Consortium, London, U.K., 25 June 2009.
- 161) *Exposure Biology: Modern Methods Tackle an Old Problem*, keynote address, Sixth International Conference on Innovations in Exposure Assessment (X2009), Boston, MA, 17 August 2009.
- 162) *Human Benzene Metabolism Following Occupational and Environmental Exposures*, Benzene 2009: Health Effects and Mechanisms of Bone Marrow Toxicity Implications for t-AML and the Mode of Action Framework, Munich, Germany, 8 Sept. 2009.

- 163) *Using Environmental Measurements and Biomarkers to Investigate Human Metabolism of Benzene*, Symposium in Appreciation of the Contributions of Bernard T. Golding, Newcastle University, Newcastle upon Tyne, U.K., 11 Sept. 2009.
- 164) *The Exposome - A Powerful Concept for Evaluating Environmental Causes of Human Diseases*, Mind and Biology: Mechanisms and Models Seminar Series, Health Psychology Program, University of California, San Francisco, CA, 13 November 2009.
- 165) *Frontiers in Exposure Science*, Emerging Science for Environmental Health Decisions Workshop: The Exposome: A Powerful Approach for Evaluating Environmental Sources of Human Disease, National Academy of Sciences, Washington, D.C., 25 Feb. 2010.
- 166) *Adductomics: Promises and Pitfalls*, Emerging Science for Environmental Health Decisions Workshop: The Exposome: A Powerful Approach for Evaluating Environmental Sources of Human Disease, National Academy of Sciences, Washington, D.C., 25 Feb. 2010.
- 167) *Using Adducts of Serum Albumin for Carcinogen Discovery*, Workshop on The Future of Molecular Epidemiology: New Tools, Biomarkers, and Opportunities, American Association for Cancer Research, Miami, FL. 6-9 June, 2010.
- 168) *Exposure, Biomarkers of Exposure, Exposure Biology, and the Exposome*, Center for Research in Environmental Epidemiology, Barcelona, Spain, 23 July 2010.
- 169) *Exposure, Exposure Biology, and the Exposome*, Occupational and Environmental Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden, 1 Sept. 2010.
- 170) *Using Albumin Adducts in Neonatal Blood Spots to Characterize Gestational Exposures*, Keynote address at the Eighth International Symposium on Biological Monitoring in Occupational and Environmental Health, Helsinki, Finland, 6-8 Sept. 2010.
- 171) *Footprints of Chemical Exposure: The Adductome*, Keynote address at the Sixth Annual Symposium on Predictive Health, Human Health: Molecules to Mankind, Emory University, Atlanta, GA 13-14, Dec. 2010.
- 172) *The Exposome Concept*, Exposome Meeting, MRC-HPA Centre for Environment and Health, Imperial College, London, U.K., 25 Feb. 2011.
- 173) *The Exposome Concept*, Envirogenmarkers 2nd Annual General Meeting and Workshop on the Exposome, Athens, Greece, 28 Feb. – 2 March, 2011.
- 174) *Adductomics: a Tool for Discovering Exposures to Toxic Chemicals*, Clinica del Lavoro, University of Milan, Milan, Italy, 18 May 2011.
- 175) *Exposure Biology and the Exposome: a Health-Based Paradigm for Exposure Science*, Special Joint Session on Emerging Exposure Science for Developing Chemical Regulatory Policy, sponsored by the Society of Environmental Toxicology and Analytical Chemistry (SETAC) Europe and the International Society of Exposure Science (ISES), Milan, Italy, 20 May, 2011.
- 176) *Exposure Biology and the Exposome*, keynote address, International Symposium for Exposure Biology for Environmental Contaminants: from Exposure to Health Effects, Seoul National University, Korea, 10-11 October 2011.
- 177) *Exposure Science, Past, Present and Future*, keynote address, Symposium on Exposure Sciences in Environmental Health, Korean Society of Environmental Health, Seoul, Korea, 14 October 2011.
- 178) *Expanding the Scope of Exposure Science*, Wesolowski Award Lecture, International Society of Exposure Science, Annual Meeting, Baltimore, MD, 26 October 2011.
- 179) *Using -Omics Methods to Characterize Individual Exposomes*, Emerging Science for Environmental Health Decisions Workshop: Emerging Technologies for Measuring Individual Exposomes, National Academy of Sciences, Washington, D.C., 8 Dec. 2011.
- 180) *Using Exposome-Wide Association Studies (EWAS) to Discover Environmental Causes of Disease*, Workshop on Tackling the Effect of Environmental Exposures on Chronic Disease, U.K. Medical Research Council, London, U.K. 20 Feb. 2012.
- 181) *Protein Adducts as Biomarkers of Exposure to Reactive Electrophiles – Targeted and Untargeted Approaches*, King's College London, School of Biomedical Sciences, London, U.K. 22 Feb. 2012.
- 182) *Exposure Biology: from Benzene to the Exposome*. California Department of Public Health, Richmond, CA, 27 Feb. 2012.

- 183) *Discovering Environmental Causes of Disease*, Friend E. Clark Lecture, Dept. of Chemistry, University of West Virginia, Morgantown, WV, 6 March 2012.
- 184) *Using Protein Adducts to Investigate Human Exposures to Reactive Electrophiles*, Friend E. Clark Lecture, Dept. of Chemistry, University of West Virginia, Morgantown, WV, 7 March 2012.
- 185) *Discovering Environmental Causes of Disease: from Exposure Biology to the Exposome*, webinar presented to the U.S. EPA CompTox Communities of Practice, Research Triangle Park, NC, 26 April 2012.
- 186) *Implications of Low-dose Benzene Metabolism for Human Risk Assessment*, Eurotox Annual Conference, Stockholm, Sweden, 18 June 2012.
- 187) *Adductomics: Evaluating Exposures to Reactive Electrophiles*, Department of Materials and Environmental Chemistry, Arrhenius Laboratory, Stockholm University, Sweden, 20 June 2012.
- 188) *Using Exposome-wide Association Studies (EWAS) to Discover Environmental Causes of Disease*, keynote address, Kenneth Rainin Foundation Symposium on Human Evolution and Chronic Diseases, Chicago, IL, 20 July 2012.
- 189) *Exposome-wide Association Studies (EWAS) for Discovering Environmental Causes of Disease*, Superfund Research Program 25th Anniversary Meeting, Raleigh, NC, 24 Oct. 2012.
- 190) *Using Exposome-wide Association Studies (EWAS) to Discover Causes of Cancer*, keynote address, Toward Precision Cancer Care: Biobehavioral Contributions to the Exposome, workshop sponsored by the American Psychosomatic Society, Chicago, IL, 26 Oct. 2012.
- 191) *Introduction to the Exposome Concept (Part 1 – EWAS)*, keynote address, kickoff meeting of the Exposomics Project, International Agency for Research on Cancer, Lyon, France, 26 Nov. 2012.
- 192) *Omics Open Doors to Useful Biomarkers*, keynote address, UKMEG/ECNIS2-sponsored Workshop on Design of Future Molecular Epidemiology Studies and New Biomarkers, London, U.K., 30 Nov. 2012.
- 193) *The Exposome: Key to Biomarker Discovery*, round-table discussion - Do we need the exposome?, Department of Epidemiology and Biostatistics, Imperial College, London, 4 Dec. 2012.
- 194) *Exposing the Exposome*, invited lecture, International Agency for Research on Cancer, Lyon, France 5 March 2013.
- 195) *Adductomics: Evaluating Exposures to Reactive Electrophiles*, invited lecture, International Agency for Research on Cancer, Lyon, France, 24 April 2013.
- 196) *Exposing the Exposome*, invited lecture, ‘specialists’ meeting on the exposome, EDF Service des Etudes Médicales, Levallois-Perret (Paris), France, 31 May 2013.
- 197) *History of Exposure Assessment*, lecture, course on “Frontiers of exposure assessment in epidemiology: exposomics,” European Educational Programme in Epidemiology, Florence, Italy, 17-21 June 2013.
- 198) *The Exposome*, lecture, course on “Frontiers of exposure assessment in epidemiology: exposomics,” European Educational Programme in Epidemiology, Florence, Italy, 17-21 June 2013.
- 199) *Exposome-wide Association Studies*, lecture, course on “Frontiers of exposure assessment in epidemiology: exposomics,” European Educational Programme in Epidemiology, Florence, Italy, 17-21 June 2013.
- 200) *Biomonitoring and Exposure Biology*, lecture, course on “Frontiers of exposure assessment in epidemiology: exposomics,” European Educational Programme in Epidemiology, Florence, Italy, 17-21 June 2013.
- 201) *The Microbiome*, lecture, course on “Frontiers of exposure assessment in epidemiology: exposomics,” European Educational Programme in Epidemiology, Florence, Italy, 17-21 June 2013.
- 202) *A Vision for Metabolomics in Research on the Exposome*, Progress in metabolomics for clinical and epidemiological research: a joint discussion with IARC, CRMN and SCA, International Agency for Research on Cancer, Lyon, France 25 June 2013.
- 203) *The Exposome and Environmental Epidemiology*, keynote address for the Workshop on the Food Metabolome and Biomarkers for Dietary Exposure, Metabolomics 2013, Glasgow, U.K. 4 July 2013.
- 204) *What is the exposome?* Webinar presented to the Collaborative on Health and the Environment, entitled, The Exposome: Measuring Multiple Factors Impacting Our Health, 18 September 2013.

- 205) *Using Untargeted Mass Spectrometry to Explore the Exposome*, presented at the symposium entitled Seeing the Whole Picture: Moving Toward Methods that Can Detect More Chemicals, University of California, Berkeley Superfund Research Program, Berkeley, CA, 20 September 2013.
- 206) *What is the exposome?* Keynote lecture, Environmental Mutagens and Genomics Society, annual meeting, Monterey, CA 23 September 2013.
- 207) *Exposing the Exposome*, Division of Environmental Health, Keck School of Medicine, University of Southern California, Los Angeles, CA, 1 November 2013.
- 208) *The Exposome: Discovering Causes of Chronic Diseases*, Agilent Technologies, Santa Clara, CA, 7 November 2013.
- 209) *Interrogating the Exposome to Discover Causes of Chronic Diseases*, Department of Environmental Health, Boston University School of Public Health, Boston, MA, 5 December 2013.
- 210) *The Exposome Exposed: The Future of Environmental Health?* Centennial James Whittenberger Lecture, Department of Environmental Health, Harvard School of Public Health, Boston, MA, 6 December 2013.
- 211) *Using Dried Blood Spots to Investigate in utero Exposures*, EPA/NIEHS Children's Centers Webinar, 7 January 2014.
- 212) *Interrogating the Exposome to Discover Causes of Cancer*, American Association for Cancer Research, annual meeting, San Diego, CA, 7 April 2014.