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. 16

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. Martyn T. Smith regarding the mechanism of acrylamide-induced cancer:

3. Exhibit C - Testimony of Martyn T. Smith in CERT v. Starbucks, October 14, 2014
4. Exhibit D - Curriculum Vitae of Martyn T. Smith

Kindly include these materials of Dr. Martyn T. Smith in the record for this rulemaking proceeding.

Very truly yours,

Raphael Metzger

RM:ip
encls: as specified
EXHIBIT “A”
CERT et al. vs. Burger King et al.

Opinions of Martyn T. Smith Ph.D.

1) Cancer is seen at multiple sites in animals exposed to acrylamide.\(^1\)\(^-\)\(^5\).

2) Acrylamide is considered by authoritative bodies, such as the International Agency for Research on Cancer and the US EPA, to be a probable human carcinogen.\(^6\)\(^-\)\(^7\).

3) Acrylamide is genotoxic – it damages DNA and causes mutations in human cells.\(^6\)\(^,\)\(^8\)\(^-\)\(^47\).

4) After eating food containing acrylamide, the chemical is taken up by the body and distributed to tissues in the body and to the fetus in pregnant women.\(^21\)\(^,\)\(^48\)\(^-\)\(^58\).

5) Eating one portion of French fries exposes each cell in the human body to several thousand molecules of acrylamide, on average.

6) Acrylamide is converted to the genotoxic epoxide metabolite, glycidamide by the enzyme cytochrome P4502E1 (CYP2E1).\(^25\)\(^,\)\(^26\)\(^,\)\(^59\)\(^-\)\(^62\).

7) The experimental data support a genotoxic mode-of-action for acrylamide, the absence of a threshold for carcinogenic effects and linear or supralinear effects of acrylamide in the low-dose region.\(^8\)\(^,\)\(^53\).

8) Humans will vary in their sensitivity to the toxic effects of acrylamide, because of differences in CYP2E1 levels and other factors, which should be accounted for in the risk assessment process.\(^25\)\(^,\)\(^35\)\(^,\)\(^61\)\(^,\)\(^64\)\(^-\)\(^65\).

9) I concur with the World Health Organization which recognizes “the presence of acrylamide in food as a major concern in humans based on the ability to induce cancer and heritable mutations in laboratory animals.”
2. Bull RJ, Robinson M, Stober JA. Carcinogenic activity of acrylamide in the skin 
3. Friedman MA, Dulak LH, Stoeham MA. A lifetime oncogenicity study in rats 
study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol Appl 
7. NTP-CERHR Monograph on the Potential Human Reproductive and 
Developmental Effects of Acrylamide. Nip Cerhr Mon. 2005;i-III76.
8. Abramsson-Zetterberg L. The dose-response relationship at very low doses of 
acrylamide is linear in the flow cytometer-based mouse micronucleus assay. Mutat Res. 
9. Abramsson-Zetterberg L, Wong J, Ilback NG. Acrylamide tissue distribution and 
genotoxic effects in a common viral infection in mice. Toxicology. 2005;211:70-76.
11. Besaratinia A, Pfeifer GP. Weak yet distinct mutagenicity of acrylamide in 
13. Besaratinia A, Pfeifer GP. DNA adduction and mutagenic properties of 
Carcinogenesis. 2007;28:519-528.
15. Blasiak J, Gloc E, Wozniak K, Czechowska A. Genotoxicity of acrylamide in 
carcinogenic agent, induces DNA damage in rat thyroid cell lines and primary cultures. 
17. Cibak R, Vortorkova M. Cytogenetic effects of acrylamide in the bone marrow 
18. Cibak R, Vortorkova M. Activity of acrylamide in single-, double-, and triple-
19. Dearfield KL, Abernathy CO, Ottley MS, Brantner JH, Hayes PF. Acrylamide: its 
metabolism, developmental and reproductive effects, genotoxicity, and carcinogenicity. 
Mutat Res. 1988;195:45-77.


22. Favor J, Shelby MD. Transmitted mutational events induced in mouse germ cells following acrylamide or glycidamide exposure. Mutat Res. 2005;580:21-30.


44. Xiao Y, Tates AD. Increased frequencies of micronuclei in early spermatids of rats following exposure of young primary spermatocytes to acrylamide. Mutat Res. 1994;309:245-253.
EXHIBIT “B”
CERT vs. Starbucks

Opinions of Martyn Smith

1) Cancer is seen at multiple sites in animals exposed to acrylamide [1-8].

2) Acrylamide is considered by authoritative bodies, such as the International Agency for Research on Cancer, the National Toxicology Program and the US EPA, to be a probable human carcinogen [9, 10].

3) Acrylamide is converted to the genotoxic epoxide metabolite, glycidamide, mainly by the enzyme cytochrome P4502E1 (CYP2E1) [11-20].

4) Glycidamide carcinogenicity is remarkably similar to that produced by acrylamide and glycidamide is the probable carcinogenic metabolite of acrylamide [6, 7, 21].

5) Acrylamide and its metabolite glycidamide are genotoxic – they damage DNA and cause mutations [12, 14, 22-57].

6) The most important form of genotoxicity for cancer induction is more likely than not clastogenicity, which breaks the chromosomes and causes structural chromosome aberrations and micronucleus formation [20, 58, 59]. Chromosome aberrations and micronuclei have been shown to be predictive of future cancer risk [60-63].

7) One mechanism by which acrylamide likely induces clastogenicity is via the inhibition of topoisomerase II [64]. Clastogenicity has been shown to be linear to low doses for several classical clastogens [65].
8) The experimental data support a genotoxic mode-of-action for acrylamide, the absence of a threshold for carcinogenic effects and linear or supralinear effects of acrylamide in the low-dose region[22, 37, 66].

9) After consuming food and beverages containing acrylamide, the chemical is taken up by the body and distributed to tissues in the body and to the fetus in pregnant women [18, 34, 67-75].

10) Humans vary in their sensitivity to the toxic effects of acrylamide, because of differences in CYP2E1 levels and other factors, which should be accounted for in the risk assessment process.

11) I concur with the World Health Organization which recognizes “the presence of acrylamide in food as a major concern in humans based on the ability to induce cancer and heritable mutations in laboratory animals.”

References


EXHIBIT “C”
APPEARANCES:

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CASE NUMBER: BC435759

CASE NAME: CERT VS. STARBUCKS

DEPARTMENT: 323 HON. ELIHU M. BERLE

REPORTER: DANA SHELLEY, RPR, CSR #10177

LOS ANGELES, CALIFORNIA TUESDAY, OCTOBER 14, 2014

TIME: 9:19 A.M.

APPEARANCES: (AS HERETOFORE NOTED.)

THE COURT: GOOD MORNING, COUNSEL. BACK ON THE
RECORD IN CERT VS. STARBUCKS.

ALL COUNSEL ARE PRESENT, AND MR. METZGER WAS
READY TO CALL HIS NEXT WITNESS.

MR. METZGER: YES, YOUR HONOR. THE PLAINTIFF
WOULD CALL PROFESSOR MARTYN SMITH.

THE COURT: PROFESSOR SMITH, PLEASE COME FORWARD.

THE CLERK: SIR, WOULD YOU RAISE YOUR RIGHT HAND
TO BE SWORN.

MARTYN THOMAS SMITH,
CALLED AS A WITNESS BY THE PLAINTIFF, WAS SWORN AND
TESTIFIED AS FOLLOWS:

THE CLERK: THANK YOU. PLEASE BE SEATED. WILL
YOU STATE AND SPELL YOUR NAME FOR THE RECORD.

THE WITNESS: MY NAME IS MARTYN, M-A-R-T-Y-N,

THE CLERK: THANK YOU.

THE COURT: GOOD MORNING, PROFESSOR SMITH.

MR. METZGER, PLEASE PROCEED.
MR. METZGER: THANK YOU, YOUR HONOR.

DIRECT EXAMINATION

BY MR. METZGER:

Q   GOOD MORNING, PROFESSOR SMITH.
A   GOOD MORNING, MR. METZGER.
Q   YOU ARE A PROFESSOR OF WHAT?
A   I'M A PROFESSOR OF TOXICOLOGY AT THE UNIVERSITY OF CALIFORNIA AT BERKELEY.
Q   OKAY. HOW LONG HAVE YOU BEEN A PROFESSOR OF TOXICOLOGY AT BERKELEY?
A   32 YEARS.
Q   I'M GOING TO SHOW YOU WHAT'S BEEN MARKED AS EXHIBIT 331. AND I'LL ASK YOU TO CONFIRM THAT THIS IS A COPY OF YOUR CURRICULUM VITAE.
A   IT IS.

(EXHIBIT 331 MARKED FOR IDENTIFICATION.)

Q   BY MR. METZGER: OKAY. AND DOES IT SET FORTH YOUR PROFESSIONAL QUALIFICATIONS, YOUR EDUCATION, TRAINING, AND EXPERIENCE?
A   IT DOES, AS OF APRIL OF THIS YEAR.
Q   DOES IT ALSO INCLUDE A LIST OF YOUR PUBLICATIONS?
A   IT DOES.
Q   NOW, DID YOU PREPARE A LIST OF OPINIONS FOR THIS CASE REGARDING THE OPINIONS THAT YOU HAVE FORMED REGARDING ACRYLAMIDE?
A   I DID.
Q AND I'LL SHOW YOU WHAT'S BEEN MARKED AS
EXHIBIT 32. IS THAT THE LIST OF OPINIONS, WITH
REFERENCES -- SUPPORTING REFERENCES?
A IT IS.

(EXHIBIT 32 MARKED FOR IDENTIFICATION.)

MR. METZGER: YOUR HONOR, I WOULD OFFER THE
CURRICULUM VITAE, EXHIBIT 331, IN EVIDENCE.
THE COURT: ANY OBJECTION?
MR. SCHURZ: NO OBJECTION, YOUR HONOR.
THE COURT: ALL RIGHT. EXHIBIT 331 IS IN
EVIDENCE.

(EXHIBIT 331 RECEIVED IN EVIDENCE.)

Q BY MR. METZGER: AND HAVE YOU PREPARED A
POWERPOINT PRESENTATION TO FACILITATE THE RENDITION OF
YOUR TESTIMONY AT TRIAL?
A I HAVE.
Q IS THAT EXHIBIT 352?
A YES.

(EXHIBIT 352 MARKED FOR IDENTIFICATION.)

Q BY MR. METZGER: ALL RIGHT. HAVE YOU
DIRECTED A LABORATORY AT UC BERKELEY?
A YES. I DIRECT THE GENES AND ENVIRONMENT
LABORATORY, ALONG WITH PROFESSORS RAPPAPORT AND LUOPING
ZHANG.
Q AND WHAT IS THE GENES AND ENVIRONMENT
LABORATORY? WHAT DOES IT DO?
A IT AIMS TO UNDERSTAND THE INTERACTIONS
BETWEEN OUR GENES AND THE ENVIRONMENT AND ENVIRONMENTAL
EXPOSURES AND TO UNDERSTAND HOW TOXIC CHEMICALS ACT IN
THE HUMAN BODY.

Q HAVE YOU DIRECTED A SUPERFUND RESEARCH
PROGRAM AT UC BERKELEY?
A YES, SINCE 1986.
Q AND WHAT IS THAT PROGRAM?
A IT'S A PROGRAM TO STUDY THE HEALTH EFFECTS
OF TOXIC SUBSTANCES FOUND AT SUPERFUND SITES AND ALSO TO
DEVELOP METHODS FOR THEIR REMEDIATION AND TREATMENT.
Q WOULD YOU TELL US WHAT POSITIONS YOU'VE HELD
AT UC BERKELEY.
A I CAME AS AN ASSISTANT PROFESSOR OF
TOXICOLOGY IN 1982. I WAS PROMOTED TO TENURE IN 1987
AND THEN TO FULL PROFESSOR IN 1992. I'VE HELD VARIOUS
POSITIONS WITHIN THE UNIVERSITY, INCLUDING MOST RECENTLY
DIRECTOR OF THE BERKELEY INSTITUTE OF ENVIRONMENT.
I'VE ALSO SERVED ON THE GRADUATE COUNCIL AS
THE VICE CHAIR, WHICH OVERSEES ALL GRADUATE EDUCATION AT
BERKELEY. I'VE CHAIRED THE FACULTY OF THE SCHOOL OF
PUBLIC HEALTH.
AND I'VE SERVED AS HEAD OF MY DIVISION,
WHICH IS SOMETHING WE ROTATE AMONGST SENIOR COLLEAGUES.
AND I'VE BEEN DIRECTOR, AS YOU MENTIONED, OF THE
SUPERFUND RESEARCH PROGRAM AT BERKELEY -- WHICH IS THE
LARGEST FEDERAL GRANT ON THE CAMPUS -- FOR THE LAST 27
YEARS OR SO.
Q HOW LARGE IS THAT GRANT?
A IT'S $2.5 MILLION PER YEAR. IT'S AUDITED
Almost every year by the federal government because of its size, and it's a large -- takes a lot of my time to manage such a grant.

Q Okay. You mentioned your division. What division is that?

A It's the Division of Environmental Health Sciences, within the School of Public Health.

Q Okay. Have you seen a biographical summary of you that has been posted on the UC website?

A I have.

Q And does that include a description of your research interests?

A It does.

Q All right. I have taken the liberty of bullet-pointing those. I'd like to go over them with you.

Biomarkers of Carcinogenesis. Would you tell us what that is and what your research in that area has been.

A Carcinogenesis is the development of cancer in living organisms, including humans. And we would like to obtain biomarkers, where we take a sample of blood or some other easily accessible tissue, and predict who is going to get cancer. That's what the first area is about.

Q And how long has that been a research interest of yours?

A For over 20 years.
Q THE NEXT ONE IS DIET AS A RISK FACTOR FOR CANCER. TELL US ABOUT THAT, PLEASE.

A YES. I'VE BEEN INTERESTED IN DIETARY DEFICIENCIES, LIKE LOW FOLATE, AND ALSO CHEMICALS IN THE DIET, SUCH AS FLAVENOIDS -- WHICH ARE CLASSIC COMPOUNDS, FOUND IN EVERYTHING FROM RED WINE TO COFFEE TO FRUITS AND VEGETABLES -- AS RISK FACTORS FOR CANCER.

AND I'VE BEEN INTERESTED IN THE PROTECTION AND THE THINGS -- PROTECTION FROM CANCER OF THINGS IN THE DIET, AND ALSO POSSIBLE CARCINOGENS WITHIN THE DIET.

Q OKAY. THE NEXT ONE IS BIOMARKERS OF BENZENE EXPOSURE AND GENOTOXICITY. TELL US ABOUT YOUR RESEARCH IN THAT AREA.

A THAT'S THE WORK THAT I'M BEST KNOWN FOR. BENZENE IS A COMPONENT OF GASOLINE AND IS ALSO FOUND AT SUPERFUND SITES. AND PEOPLE ARE EXPOSED IN REFINERIES AND OTHER SETTINGS.

WE HAVE DEVELOPED METHODS FOR MEASURING EXPOSURE OF PEOPLE TO BENZENE AND EXAMINING EARLY EFFECTS OF THAT CHEMICAL ON PEOPLE, IN A VARIETY OF STUDIES THAT WERE PERFORMED IN CHINA AND OTHER COUNTRIES, THAT HAS LED TO ALTERED REGULATIONS IN THE UNITED STATES.

Q CHILDHOOD LEUKEMIA AND ENVIRONMENTAL EXPOSURES. TELL US ABOUT YOUR RESEARCH IN THAT AREA.

A WELL, BENZENE IS A KNOWN CAUSE OF LEUKEMIA. WE BECAME INTERESTED IN BENZENE BEING A POSSIBLE CAUSE OF CHILDHOOD LEUKEMIA AND BECAME GENERALLY INTERESTED IN
THE CAUSE OF THE CHILDHOOD LEUKEMIA.

AND WITH PATRICIA BUFFLER, I BEGAN A LARGE STUDY IN CALIFORNIA OF CHILDHOOD LEUKEMIA THAT BEGAN IN 1995, THROUGH THE SUPERFUND PROGRAM. WE'VE BEEN EXAMINING MANY DIFFERENT TYPES OF ENVIRONMENTAL EXPOSURE IN RELATION TO THE INCIDENCE OF CHILDHOOD LEUKEMIA IN CALIFORNIA.

Q TELL US ABOUT YOUR RESEARCH INTO MOLECULAR EPIDEMIOLOGY OF NON-HODGKIN LYMPHOMA.

A SO LYMPHOMA IS A CANCER OF THE LYMPH NODES, VERY SIMILAR TO A LEUKEMIA BUT NOT QUITE THE SAME. AND IT HAS -- IT APPEARS TO HAVE SIMILAR RISK FACTORS BUT ALSO SOME DIFFERENT ONES.

AND I BECAME INVOLVED WITH A LARGE CONSORTIUM CALLED THE INTERLYMPH CONSORTIUM, WHICH IS THE STUDIES OF -- ALL STUDIES IN THE WORLD OF NON-HODGKIN LYMPHOMA. AND WE ATTEMPTED TO FIND THE GENETIC AND ENVIRONMENTAL CAUSES OF NON-HODGKIN LYMPHOMA, AND I'VE PUBLISHED MANY PAPERS ON THAT.

Q OKAY. LASTLY, STUDIES OF ENVIRONMENTAL MUTAGENS AND CARCINOGENS. TELL US ABOUT THAT.

A WE ALSO CONDUCT WORK IN THE LABORATORY WHERE WE STUDY THE EFFECTS OF CHEMICALS FOUND IN THE ENVIRONMENT WHICH ARE POTENTIALLY CARCINOGENIC AND ALSO CAN DAMAGE THE DNA AND CAUSE MUTATIONS, WHICH IS MUTAGENS. WE STUDY THEM IN A PETRIE DISH, BASICALLY, IN CELL CULTURES USING HUMAN CELLS.

Q DOES THE BIOGRAPHICAL SUMMARY ON THE UC
BERKELEY WEBSITE ALSO INCLUDE A DESCRIPTION OF YOUR EXPERTISE?

A  YES.

Q  OKAY. IT SAYS:

"DR. SMITH HAS EXPERTISE AND A BROAD BACKGROUND IN MOLECULAR EPIDEMIOLOGY, TOXICOLOGY, AND GENOMICS, AIMED AT FINDING THE CAUSES OF CHRONIC DISEASE, INCLUDING LEUKEMIA -- INCLUDING LYMPHOMA AND LEUKEMIA. HIS INTEREST IN THE SUBJECT OF BENZENE TOXICITY BEGAN IN THE MID 1980S, AND HE HAS PUBLISHED EXTENSIVELY ON THIS TOPIC, MOST RECENTLY AS A REVIEW FOR THE 2010 ANNUAL REVIEWS OF PUBLIC HEALTH."

IS THAT A FAIR DESCRIPTION OF YOUR FIELDS OF EXPERTISE?

MR. SCHURZ: I'LL INTERPOSE AN OBJECTION AS HEARSAY, READING A DOCUMENT THAT IS NOT ADMITTED INTO EVIDENCE.

THE COURT: OVERRULED.

YOU CAN ANSWER THE QUESTION.

THE WITNESS: YES, IT IS.

Q  BY MR. METZGER: OKAY. WOULD YOU TELL US ABOUT YOUR EDUCATIONAL BACKGROUND, WHERE YOU WENT TO SCHOOL.

A  SURE. WELL, I GREW UP IN NORTHERN ENGLAND AND WENT TO THE UNIVERSITY OF LONDON TO DO A DEGREE IN BIOLOGY, HAVING DECIDED NOT TO DO MEDICINE, AND BECAME
INTERESTED IN DOING RESEARCH THERE.

STARTED TO WORK IN THE KENNEDY INSTITUTE OF RHEUMATOLOGY IN LONDON. ENJOYED RESEARCH AND WAS ADVISED TO GO TO ST. BARTHOLOMEW'S HOSPITAL, WHICH HAD THE BEST BIOCHEMISTRY DEPARTMENT IN THE WORLD AT THE TIME. DID A PH.D. THERE IN 1980.

WANTING TO GET A JOB, I TALKED TO SOME OF MY MENTORS. AND THEY SAID, "WELL, YOU CAN ALWAYS DO BIOCHEMISTRY, BUT WE THINK THIS TOXIC CHEMICALS THING IS GOING TO BE A BIG THING. SO WHY DON'T YOU USE YOUR BIOCHEMICAL KNOWLEDGE IN THE AREA OF TOXICOLOGY?"

THERE WAS NOT MUCH AVAILABILITY OF TRAINING IN TOXICOLOGY IN ENGLAND AT THAT TIME, SO I WENT TO SWEDEN TO WORK AT THE KAROLINSKA INSTITUTE, WHICH GIVES OUT NOBEL PRIZES; AND WORKED WITH STEN ORRENIUS, WHO WAS CONSIDERED PROBABLY THE BEST TOXICOLOGIST IN THE WORLD AT THE TIME, AND DID POSTDOCTORAL RESEARCH WITH HIM IN 1980 TO '81.

Q ALL RIGHT. DO YOU TEACH STUDENTS AT UC BERKELEY?

A I DO.

Q WILL YOU TELL US ABOUT YOUR TEACHING ACTIVITIES.

A SO I TAUGHT -- AFTER I FINISHED IN SWEDEN, I WENT BACK TO ENGLAND AND TAUGHT THE FIRST-EVER UNDERGRADUATE DEGREE IN TOXICOLOGY IN ENGLAND AND THEN GOT RECRUITED TO BERKELEY ONE YEAR LATER, IN 1982.

SINCE THAT TIME, I'VE CONSISTENTLY TAUGHT AT
BERKELEY. WE TEACH A LARGE CLASS TO FRESHMAN AND
SOPHOMORES, INTRODUCING THEM TO THE SUBJECT OF
TOXICOLOGY. THIS CLASS VARIES BETWEEN 200 AND 400
STUDENTS EVERY YEAR.
I'VE ALSO TAUGHT FOR MANY YEARS NOW THE MAIN
CLASS, THE CORE CLASS, IN TOXICOLOGY TO GRADUATE
STUDENTS IN OUR PROGRAM.
Q WOULD YOU TELL THE COURT ABOUT SOME OF THE
ADVISORY POSITIONS THAT YOU'VE HELD.
A I MOST RECENTLY SERVED, FOR EXAMPLE, ON THE
SCIENTIFIC COUNCIL OF THE INTERNATIONAL AGENCY FOR
RESEARCH ON CANCER. I WAS THE ELECTED REPRESENTATIVE
FROM THE UNITED STATES ON THAT COUNCIL, WHICH OVERSEES
ALL SCIENCE MATTERS AT IARC, AS IT'S CALLED.
I'VE ALSO SERVED ON THE BOARDS OF VARIOUS
EUROPEAN ORGANIZATIONS AND U.S. CENTERS, AND I'VE ACTED
AS AN ADVISOR TO MANY GOVERNMENTS ON THE ISSUE OF
BENZENE.
I'VE ALSO SERVED ON THE NATIONAL ADVISORY
ENVIRONMENTAL HEALTH SCIENCES COUNCIL, WHICH ADVISES THE
NIH ON ALL THE AREAS RELATED TO ENVIRONMENTAL HEALTH.
Q WOULD YOU TELL US ABOUT SOME OF THE ELECTED
POSITIONS THAT YOU'VE HAD IN PROFESSIONAL SOCIETIES.
A WITH PROFESSIONAL SOCIETIES, I'VE ACTED WITH
THE MOLECULAR EPIDEMIOLOGY GROUP OF THE AMERICAN
ASSOCIATION FOR CANCER RESEARCH. I HAVE SERVED ON
VARIOUS ADVISORY BOARDS TO LARGE INSTITUTIONS AND
CENTERS.
Q AND WOULD YOU TELL THE COURT BRIEFLY ABOUT
SOME OF THE AWARDS AND HONORS THAT YOU'VE RECEIVED OVER
THE YEARS.

A MOST RECENTLY, I RECEIVED THE ALEXANDER
HOLLAENDER AWARD FROM THE ENVIRONMENTAL MUTAGENESIS AND
GENOMICS SOCIETY. IT'S A VERY NICE AWARD. IT'S ONE
DONE WITH THE IDEA OF REWARDING SOMEONE FOR DOING
SCIENCE IN THE INTERESTS OF PUBLIC HEALTH. AND I WAS
SPECIFICALLY CITED FOR MY WORK ON BENZENE FOR THAT.

I WAS ALSO GIVEN THE AWARD RECOGNIZING
SCIENTIFIC CONTRIBUTIONS IN THE PLENARY LECTURE AT THE
AMERICAN CHEMICAL SOCIETY THIS YEAR. AND PREVIOUSLY,
I'D RECEIVED AWARDS FROM INTERLYMPH AND FROM THE
CHILDREN'S ENVIRONMENTAL HEALTH NETWORK.

Q OKAY. WOULD YOU TELL THE COURT HOW MANY
PUBLICATIONS YOU HAVE, AND WHAT FIELDS.

A I HAVE A LITTLE OVER 300 PUBLICATIONS.
ABOUT 95 OF THEM ARE ON BENZENE. ALMOST ALL OF THEM ARE
ON THE SUBJECT OF TOXICOLOGY OR MOLECULAR OR BIOCHEMICAL
TOXICOLOGY.

I'VE WRITTEN 40 CHAPTERS FOR BOOKS, AND I'VE
EDITED ONE MAJOR BOOK FOR IARC. AND I'VE SERVED ON THE
EDITORIAL BOARDS OF NUMEROUS JOURNALS, ROTATING ON AND
OFF OF THE THOSE PARTICULAR JOURNALS.

Q I HAVE HERE A BOOK BY IARC CALLED
"MECHANISMS OF CARCINOGENESIS, IARC SCIENTIFIC
PUBLICATIONS NO. 157." AND IT HAS A CHAPTER IN HERE
ENTITLED "CAUSAL MODELS OF LEUKEMIA AND LYMPHOMA."
A YES.

Q IS THIS A CHAPTER THAT YOU WROTE UPON INVITATION FROM IARC?

A IT IS. AND I'M CURRENTLY WRITING ANOTHER ONE ON MECHANISMS OF CARCINOGENESIS FOR THE VOLUME 100 OVERVIEW.

AND I'M HELPING IARC REWRITE THE PREAMBLE TO THEIR -- WHICH IS EXTREMELY IMPORTANT IN THE WAY THAT THEY CONSIDER IDENTIFYING CARCINOGENS, BY ORGANIZING HOW THEY LOOK AT MECHANISTIC DATA.

Q ALL RIGHT. LET'S TALK ABOUT ACRYLAMIDE.

WOULD YOU TELL THE COURT WHAT I ASKED YOU TO EVALUATE FOR THIS CASE REGARDING ACRYLAMIDE.

A YOU ASKED ME TO REVIEW THE TOXICOLOGY OF ACRYLAMIDE TO HELP ADVISE ABOUT WHAT ITS LIKELY MECHANISM WAS IN PRODUCING CANCER, ABOUT ITS ABILITY TO DAMAGE DNA AND CAUSE GENETIC DAMAGE, AND TO EXAMINE THE RISK IT WOULD POSE FROM EXPOSURE TO HUMAN BEINGS.

Q OKAY. AND WHAT DID YOU CONCLUDE REGARDING THE CARCINOGENICITY OF ACRYLAMIDE, AT LEAST IN ANIMALS?

A THAT ACRYLAMIDE IS A CARCINOGEN WHICH ACTS AT MULTIPLE SITES IN EXPERIMENTAL ANIMALS, PRODUCING TUMORS IN MANY DIFFERENT TISSUES.

Q WHAT IS THE SIGNIFICANCE OF THAT?

MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT, UNDER EVIDENCE CODE 352, AS DUPLICATIVE AND REDUNDANT. DR. RAPPAPORT TESTIFIED ABOUT THIS TOPIC AT SOME LENGTH. DR. MELNICK TESTIFIED ABOUT THIS AT SOME LENGTH. THE
EXACT SLIDE THAT WE'RE LOOKING AT HERE WAS IN
RAPPAPORT'S SLIDES AT NO. 22.

WE WOULD ASK THE COURT TO EXCLUDE FURTHER
TESTIMONY AS REDUNDANT AND CUMULATIVE.

THE COURT: MR. METZGER?

MR. METZGER: I'LL TELL YOU WHAT. WE'LL JUST MOVE
ON. BECAUSE, ACTUALLY, IT'S -- DR. HUFF IS GOING TO
TESTIFY EXTENSIVELY ABOUT THE ANIMAL STUDIES. THIS IS
JUST BACKGROUND, SO WE CAN MOVE RIGHT ON.

THE COURT: OKAY.

Q BY MR. METZGER: DR. RAPPAPORT HAS ALREADY
TESTIFIED ABOUT THE TOXICOKINETICS OF ACRYLAMIDE, SO I
DON'T WANT TO REPEAT THAT WITH YOU, DR. SMITH.

BUT I WOULD LIKE TO ASK YOU ONE QUESTION,
WHICH IS: WHAT IS THE SIGNIFICANCE TO YOU, AS A
TOXICOLOGIST, OF ACRYLAMIDE BEING METABOLIZED BY THE
CYTOCHROME P450 CYP2E1 ENZYME?

A THE SIGNIFICANCE IS THAT ACRYLAMIDE ITSELF
CAN BE CONVERTED INTO SOMETHING CALLED GLYCIDAMIDE,
WHICH IS AN EPOXIDE, WHICH IS VERY REACTIVE AND CAUSES
DAMAGE TO THE DNA AND IS ALSO A CARCINOGEN.

Q OKAY. INCIDENTALLY, DR. MURRAY TOLD THE
COURT THAT GLYCIDAMIDE IS A REACTIVE OXYGEN SPECIES. IS
IT?

A NO. I WAS SURPRISED TO SEE THAT HE SAID
THAT. IT'S NOT A REACTIVE OXYGEN SPECIES. IT'S AN
ACTIVATED MOLECULE WITH OXYGEN INSERTED INTO IT, BUT IT
IS NOT WHAT WE CLASSICALLY CALL A REACTIVE OXYGEN
MR. METZGER: ALL RIGHT.

(PAUSE IN PROCEEDINGS.)

MR. METZGER: I'M ACTUALLY SKIPPING SOME THINGS, YOUR HONOR, SO JUST GIVE ME A MOMENT. IT WILL EXPEDITE.

Q ALL RIGHT. HAVE YOU PUBLISHED REGARDING ACRYLAMIDE?

A YES, WE HAVE.

Q HOW MANY ARTICLES HAVE YOU AND YOUR COLLEAGUES PUBLISHED REGARDING ACRYLAMIDE?

A WE'VE PUBLISHED TWO, IN THE LATE 1990S.

Q OKAY. AND IS THE FIRST ONE TITLED "MICRONUCLEI AND DEVELOPMENTAL ABNORMALITIES IN FOUR-DAY MOUSE EMBRYOS AFTER PATERNAL TREATMENT WITH ACRYLAMIDE"?

A IT IS.

Q WHAT DID YOU INVESTIGATE IN THAT STUDY?

A WELL, IT WAS WELL KNOWN THAT ACRYLAMIDE WOULD LEAD TO DNA DAMAGE AND CHROMOSOME DAMAGE, AND MICRONUCLEI ARE A MEASURE OF CHROMOSOME DAMAGE. IT'S ALSO KNOWN THAT IF YOU EXPOSE THE MOTHER TO ACRYLAMIDE THAT THE EMBRYO WOULD UNDERGO GENETIC DAMAGE. WHAT WAS NOT KNOWN WAS WHAT WOULD HAPPEN IF THE FATHER WAS EXPOSED TO ACRYLAMIDE.

AND SO THIS -- THESE EXPERIMENTS SHOWED THAT IF YOU EXPOSE THE FATHER TO ACRYLAMIDE AND THEN MATE THAT MALE MOUSE WITH A FEMALE MOUSE, THE GENETIC DAMAGE IN THE MALE IS PASSED ALONG TO THE EMBRYO; WHICH IS QUITE UNUSUAL AND SHOWS HOW AGGRESSIVE ACRYLAMIDE IS AT
PRODUCING GENETIC DAMAGE IN THE SPERM OF MALES.

AND VERY INTERESTINGLY, A PAPER HAS JUST BEEN PUBLISHED SHOWING THAT CYP2E1 IS PRESENT IN SPERM. AND SO THERE IS -- A WAY THAT YOU CAN GET REPRODUCTIVE ABNORMALITIES FROM ACRYLAMIDE WOULD BE EXPOSURE OF THE MALE TO ACRYLAMIDE ACTIVATION BY CYP2E1 IN THE SPERM, GENETIC DAMAGE WHICH IS THEN PASSED ON TO THE OFFSPRING.

AND SO THIS IS WHAT THIS PAPER SHOWED.

MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT AND MOVE TO STRIKE AS EVIDENCE REGARDING REPRODUCTIVE ABNORMALITIES. IT'S OUTSIDE THE SCOPE OF PHASE 1 AND HAS NO ROLE IN THESE COURT PROCEEDINGS.

THE COURT: OBJECTION OVERRULED.

Q BY MR. METZGER: LET ME ASK YOU, SPECIFICALLY: WHAT WERE YOUR FINDINGS IN THAT STUDY REGARDING MICRONUCLEI?

A THAT MICRONUCLEI WERE -- WHICH ARE INDICATORS OF CHROMOSOME DAMAGE, WERE PRESENT IN THE MOUSE EMBRYOS AFTER EXPOSURE OF THE FATHER TO ACRYLAMIDE.

Q WOULD YOU EXPLAIN TO THE COURT WHAT MICRONUCLEI ARE.

A SURE. WHEN CHROMOSOMES ARE BROKEN OR DAMAGED IN SOME WAY DURING CELL DIVISION, WHAT NORMALLY HAPPENS IS, AS THE CELL DIVIDES, THE TWO NEW NUCLEI THAT ARE FORMED SEPARATE.

IF THE CHROMOSOMES ARE DAMAGED DURING THAT PROCESS, IT'S POSSIBLE TO FORM SMALL INDIVIDUAL TINY
LITTLE NUCLEI, THAT WE CALL MICRONUCLEI, WHICH CONTAIN
FRAGMENTS OF DNA WHICH SHOULD NORMALLY BE IN THE
NUCLEUS.

SO THIS IS A SIGN OF CHROMOSOMES BEING
BROKEN OR CHROMOSOMES BEING LEFT BEHIND DURING CELL
DIVISION, WHICH IS -- WE KNOW IS A TYPICAL CARCINOGENIC
PROCESS.

Q OKAY. THE SECOND ARTICLE THAT YOU AND YOUR
COLLEAGUES PUBLISHED REGARDING ACRYLAMIDE WAS TITLED
"ACRYLAMIDE CAUSES PREIMPLANTATION ABNORMALITIES IN
EMBRYOS AND INDUCES CHROMATIN ADDUCTS IN MALE GERM CELLS
OF MICE."

WOULD YOU TELL THE COURT WHAT THAT RESEARCH
WAS ABOUT AND WHAT IT SHOWED.

A IT'S A FOLLOW-UP TO THE EARLIER WORK, AND IT
SHOWS THAT IN THE MALE GERM CELLS, THE SPERM AND THEIR
PRECURSORS, THAT THE ACRYLAMIDE GOES AND BINDS TO THE
PROTEINS WHICH ARE ASSOCIATED WITH THE DNA, WHICH IS
CALLED CHROMATIN.

AND SO IT SHOWS THAT THE ACRYLAMIDE REACHES
THE MALE GERM CELLS AND BINDS TO -- WITHIN THEM. AND
THese ADDUCTS WILL PRODUCE CHROMOSOME DAMAGE, WHICH THEN
APPEARS TO BE TRANSFERRED ON INTO THE EMBRYO AND LEADS
TO THESE ABNORMALITIES, DEVELOPMENTAL ABNORMALITIES, IN
THE EMBRYOS.

Q OKAY.

A SO IT SHOWS AGAIN THAT EXPOSURE OF THE
FATHER WILL LEAD TO EFFECTS IN THE EMBRYO.
Q AND WHAT, FROM THESE STUDIES THAT YOU DID, RELATES TO ACRYLAMIDE AND CANCER, IF ANYTHING?

A WELL, IT ALSO SHOWS THAT ACRYLAMIDE WOULD LIKELY BE A CARCINOGEN THAT CROSSES THE PLACENTA, EITHER BY -- THROUGH EFFECTS ON THE MALE OR EFFECTS ON THE FEMALE. AND THE EXPOSURE OF THE PARENTS COULD LEAD TO DEVELOPMENTAL CHANGES IN THE OFFSPRING AND CANCER IN THE OFFSPRING.

Q OKAY. AND WHAT IS IT ABOUT THESE STUDIES THAT LEAD YOU TO CONCLUDE THAT THESE CHANGES COULD LEAD TO CANCER IN THE OFFSPRING?

A BECAUSE THE CHANGES ARE GENETIC IN NATURE. THEY'RE BINDING TO THE DNA CHROMATIN, AND THEY ARE FORMING MICRONUCLEI, WHICH ARE EVIDENCE OF CHROMOSOME BREAKS AND CHROMOSOME DAMAGES.

THE COURT: MAY I ASK THIS: WHAT DO YOU MEAN BY "EXPOSURE TO ACRYLAMIDE"?

THE WITNESS: IN THIS CASE, WE'RE ACTUALLY USING FAIRLY HIGH DOSES OF ACRYLAMIDE AND EXPOSING THE ANIMALS TO IT. I FORGET EXACTLY HOW, WHETHER WE GAVE IT BY ORAL DOSING OR BY INJECTION. BUT WE ARE GIVING THE ACRYLAMIDE AS PURE CHEMICAL.

THE COURT: PURE ACRYLAMIDE?

THE WITNESS: YES.

THE COURT: DOES IT MAKE A DIFFERENCE IF THE ACRYLAMIDE IS DILUTED IN SOME LIQUID FORM?

THE WITNESS: IT PROBABLY IS IN A LIQUID FORM AS WE ADMINISTER IT, BUT IT'S NOT MIXED WITH ANYTHING ELSE.
THE COURT: THE EXTENT OF DILUTION, DOES THAT AFFECT IT AT ALL?

THE WITNESS: THERE WILL BE A DOSE. AS YOU LOWER -- AS YOU DILUTE IT OUT, YOU WILL GET LESS EFFECT.

THE COURT: THANK YOU.

COUNSEL.

Q     BY MR. METZGER: DR. SMITH, ARE THERE DIFFERENT TYPES OF GENOTOXICITY?

A     YES, THERE ARE. "GENOTOXICITY" GENERALLY MEANS DAMAGE TO THE DNA OR TO THE GENETIC MATERIALS. AND SO YOU CAN HAVE ALL SORTS OF DAMAGE TO THE DNA.

YOU CAN HAVE INDIVIDUAL STRANDS BROKEN, WHICH IS CALLED SINGLE-STRAND BREAKS. YOU CAN BREAK BOTH STRANDS OF DNA, WHICH IS CALLED DOUBLE-STRAND BREAKS. YOU CAN CHANGE THE SEQUENCE OF THE DNA. YOU CAN INSERT BASES INTO THE DNA. YOU CAN CROSS-LINK THE DNA.

YOU CAN DO ALL SORTS OF DIFFERENT THINGS WHICH ARE REGARDED AS GENOTOXICITY.

Q     WHAT IS CLASTOGENICITY?

A     SO CLASTOGENICITY IS -- SO GENOTOXICITY IS DAMAGE AT ANY LEVEL; BASICALLY, AT THE INDIVIDUAL BASES OF THE DNA, ALL THE WAY UP TO LOSING THE WHOLE CHROMOSOMES AND GAINING CHROMOSOMES.

CLASTOGENICITY IS ONE FORM OF GENOTOXICITY, WHICH -- IT RefERS TO THE BREAKAGE OF CHROMOSOMES, WHERE THE STRANDS OF THE DNA HAVE BEEN BROKEN, AND THE CHROMOSOMES ARE FRAGMENTED IN SOME FASHION.
Q WHAT IS THE TOXICOLOGICAL SIGNIFICANCE OF A CHEMICAL BEING A CLASTOGEN?

A THOSE CHEMICALS WILL BE ABLE TO PRODUCE WHAT WE CALL STRUCTURAL CHROMOSOME ABERRATION. SO AS THE CELL TRIES TO REPAIR THE BREAKS IN THE CHROMOSOMES, AS IT GOES THROUGH CELL DIVISION, IT WILL REALIGN THEM INCORRECTLY, USUALLY.

AND THIS LEADS TO WHAT WE CALL CHROMOSOME ABERRATIONS, WHICH YOU CAN SEE UNDER A MICROSCOPE. PART OF THE CHROMOSOME IS IN THE WRONG PLACE, OR THERE'S A GAP, OR THERE'S SOME SORT OF BREAK IN IT.

AND THESE CHROMOSOME ABERRATIONS HAVE BEEN ASSOCIATED WITH FUTURE RISK OF CANCER.

Q WHEN YOU SAY, "THESE ABERRATIONS HAVE BEEN ASSOCIATED WITH FUTURE RISK OF CANCER," HOW DO YOU KNOW THAT?

A OKAY. SO THE EARLIER STUDIES WERE DONE -- WELL, THERE'S BEEN A LONG THEORY THAT CHROMOSOME BREAKAGE AND CANCER -- WAS IMPORTANT IN THE DEVELOPMENT OF CANCER. THIS IS SOMETHING THAT'S BEEN KNOWN FOR A HUNDRED YEARS. BUT AS A PREDICTER, IT WAS NOT KNOWN.

AND IT TURNED OUT THAT IN THE SCANDINAVIAN COUNTRIES, THEY HAD COLLECTED -- OR DONE CHROMOSOME ABERRATION ANALYSIS ON VERY LARGE NUMBERS OF PEOPLE, AND THEY WERE ABLE TO THEN FOLLOW THOSE PEOPLE OVER 20 OR 30 OR MORE YEARS AND LOOK AT WHO DEVELOPED CANCER.

AND WHEN THEY DID THAT, THEY FOUND THAT THOSE WHO HAD A HIGH LEVEL OF CHROMOSOME ABERRATIONS 20
TO 30 YEARS BEFORE DEVELOPING CANCER WERE AT HIGHER RISK
OF DEVELOPING THOSE CANCERS -- THINGS LIKE LUNG CANCER,
LEUKEMIAS, OTHER THINGS -- THAN THE GENERAL -- THOSE
WITH A LOWER LEVEL.

THIS WAS SUBSEQUENTLY FOLLOWED UP IN ITALY,
WHERE THEY HAD SIMILARLY DONE VERY LARGE STUDIES OF
MEASURING CHROMOSOME ABERRATIONS JUST IN THE GENERAL
POPULATION. AND THEN THEY WERE ABLE TO LOOK UP THE
RECORDS AND SEE WHO GOT CANCER AND WHO DIDN'T.

AND AGAIN, IT WAS A FINDING THAT HAVING
CHROMOSOME ABERRATIONS INCREASED -- PREDICTED INCREASED
RISK OF CANCER.

Q WHAT IS THE SIGNIFICANCE OF THAT TO YOU?
A WELL, BASICALLY, IT'S THE ONLY BIOMARKER WE
HAVE THAT IS PREDICTIVE OF FUTURE CANCER RISK. SO IT'S
VERY SIMILAR TO CHOLESTEROL, FOR EXAMPLE; YOUR
CHOLESTEROL RATIO AND HEART DISEASE. SO IF YOU HAVE A
HIGH LEVEL OF CHROMOSOME ABERRATIONS, THEN YOU ARE AT
INCREASED RISK OF CANCER.

Q WILL YOU TELL THE COURT SPECIFICALLY WHAT
YOU MEAN BY "CHROMOSOME ABERRATIONS." WHAT DAMAGE ARE
YOU TALKING ABOUT?
A WHAT I'M TALKING ABOUT IS, IF YOU LOOK UNDER
A MICROSCOPE, THE CHROMOSOMES SHOULD ALL BE ALIGNED AND
BE THE RIGHT SIZE, AND THERE SHOULD BE 46 OF THEM, AND
THEY SHOULD ALL LOOK INTACT.

IF THERE ARE CHROMOSOME ABERRATIONS, THERE
WILL BE CHANGES TO THOSE STRUCTURES. THERE WILL BE BITS
BROKEN OFF, BITS LOST, SHORTER CHROMOSOME; MAYBE A WHOLE CHROMOSOME LOST, MAYBE ANOTHER ONE GAINED. THERE WILL BE CLEAR DIFFERENCES.

AND WE KNOW THAT WITH CANCER, THE MORE AGGRESSIVE AND MALIGNANT IT BECOMES, THE MORE CHANGES THERE ARE IN THE CHROMOSOMES. AND THE CHROMOSOMES OF CANCER CELLS USUALLY LOOK REALLY BAD, REALLY BEATEN UP, COMPARED TO THE NORMAL CHROMOSOMES IN YOUR HEALTHY CELLS.

Q OKAY. WHAT IS THE STATE OF THE EVIDENCE -- OR SCIENTIFIC EVIDENCE REGARDING MICRONUCLEI AS BEING PREDICTIVE OF FUTURE CANCER RISK?

A SO IT'S NOW BEEN ESTABLISHED THAT MICRONUCLEI ARE ALSO PREDICTIVE OF FUTURE CANCER RISK. GIVEN THE SUCCESS OF THE STUDY WITH CHROMOSOME ABERRATIONS, AN INTERNATIONAL GROUP OF RESEARCHERS GOT TOGETHER, POOLED ALL OF THEIR DATA ON MICRONUCLEI, AND LOOKED AT WHO DEVELOPED CANCER IN THESE DIFFERENT COUNTRIES -- EVERYWHERE FROM SWEDEN, TO AUSTRALIA, TO THE UNITED STATES.

AND THEY REACHED A SIMILAR CONCLUSION: THAT MICRONUCLEI, WHICH ALSO RESULT FROM CHROMOSOME BREAKAGE AND CHROMOSOME DAMAGE, ARE ALSO PREDICTIVE OF FUTURE CANCERS.

Q AND THESE ARE STUDIES IN PEOPLE?

A THESE ARE STUDIES IN PEOPLE WHO DON'T HAVE CANCER AND THEN GO ON TO DEVELOP CANCER.

Q ALL RIGHT. HAVE YOU PUBLISHED REGARDING THE
CLASTOGENICITY OF CHEMICALS TO HUMANS?

A YES. SO ONE OF THE MECHANISMS BY WHICH BENZENE IS THOUGHT TO CAUSE LEUKEMIA IS THROUGH A CLASTOGENIC MECHANISM. AND THE SAME IS TRUE FOR IONIZING RADIATION AND FOR CANCER CHEMOTHERAPY DRUGS. THE WAY THAT THEY ARE THOUGHT TO CAUSE LEUKEMIA IS MAINLY THROUGH A CLASTOGENIC CHROMOSOME-BREAKING MECHANISM.

Q AND TELL US ABOUT THE PUBLICATIONS THAT YOU HAVE AUTHORED REGARDING THIS TOPIC.

A SO WE HAVE DONE STUDIES IN CELL CULTURE WHERE WE TOOK HUMAN CELLS FROM HUMAN BLOOD, AND WE TOOK STEM CELLS FROM CORD BLOOD. AND WE'VE EXPOSED THEM TO VARIOUS METABOLITES OF BENZENE, INCLUDING HYDROQUINONE AND CATECHOL. AND I HAVE SEEN INCREASED LEVELS OF CHROMOSOME BREAKS, OR CLASTOGENICITY, IN THOSE CELLS. WE'VE ALSO LOOKED AT PEOPLE EXPOSED TO BENZENE IN THE WORKPLACE AND HAVE SIMILARLY FOUND INCREASED LEVELS OF CHROMOSOME BREAKAGE IN THOSE INDIVIDUALS.

Q WHAT IS THE SIGNIFICANCE OF THAT RESEARCH TO YOU?

A THIS SUGGESTS OR INDICATES THAT ONE OF THE PROBABLE MECHANISMS BY WHICH BENZENE PRODUCES LEUKEMIA IS THROUGH A CLASTOGENIC CHROMOSOME-BREAKING MECHANISM, DAMAGING STEM CELLS AND BLOOD CELLS IN THE BONE MARROW AND IN THE BLOOD; AND THAT THIS LEADS TO SUBSEQUENT DEVELOPMENT OF CANCERS LIKE LEUKEMIA.
ALL RIGHT. DR. RAPPAPORT INFORMED THE COURT THAT THE TOXICOKINETIC PROCESSES OF ACRYLAMIDE WERE ALL LINEAR, BUT HE DIDN'T TALK ABOUT CLASTOGENICITY, SPECIFICALLY, I DON'T BELIEVE.

IS CLASTOGENICITY, THE BREAKAGE OF CHROMOSOMES, ALSO A LINEAR PROCESS?

A YES. THE STUDIES THAT HAVE BEEN --

MR. SCHURZ: I'LL INTERPOSE AN OBJECTION. AGAIN, IT'S REDUNDANT. AND I'D MOVE TO EXCLUDE IT UNDER 352.

THE LINEARITY OF RELATIONSHIPS OF ACRYLAMIDE WAS A TOPIC OF DR. RAPPAPORT'S TESTIMONY, RATHER EXTENSIVELY. AND WE WOULD URGE -- OBJECT TO ANY FURTHER EVIDENCE WITH RESPECT TO THIS ISSUE AS CUMULATIVE AND REDUNDANT.

THE COURT: MR. METZGER?

MR. METZGER: I'M ASKING SPECIFICALLY ABOUT -- NOT JUST GENERALLY ABOUT ACRYLAMIDE, BUT SPECIFICALLY ABOUT THE CLASTOGENICITY OF ACRYLAMIDE, WHICH IS DR. SMITH'S FIELD OF EXPERTISE. AND I DO NOT BELIEVE THAT DR. RAPPAPORT TESTIFIED ABOUT THIS PARTICULAR PIECE OF IT.

THE COURT: ALL RIGHT. OBJECTION OVERRULED FOR NOW.

Q BY MR. METZGER: DO YOU HAVE THE QUESTION IN MIND?

A NO. COULD WE DO IT AGAIN?

Q SURE. IS CLASTOGENICITY ALSO A LINEAR PROCESS?

A IN THE STUDIES THAT HAVE BEEN DONE -- WHERE
THEY'VE BEEN ABLE TO EXAMINE CLASTOGENICITY USING WHAT WE CALL A FLOW CYTOMETER, A VERY SENSITIVE MACHINE, DOWN TO VERY LOW LEVELS -- IT'S BEEN SHOWN THAT OVER A LARGE DOSE RANGE, CLASTOGENS ACT IN A LINEAR FASHION, INCLUDING ACRYLAMIDE.

Q AND WHAT IS THE SIGNIFICANCE OF CLASTOGENICITY OF ACRYLAMIDE BEING LINEAR AT VERY LOW DOSES?

A IT MEANS THAT IF YOU EXTRAPOLATE DATA FROM RELATIVELY HIGHER DOSES IN EXPERIMENTAL ANIMALS OR IN WORKERS OR HUMANS EXPOSED TO HIGH LEVELS OF ACRYLAMIDE, THEN YOU SHOULD USE A LINEAR TYPE OF MATHEMATICAL MODEL, WHERE YOU DRAW THE LINES STRAIGHT BACK TO LOWER DOSES IN PREDICTING THE RISK.

MR. SCHURZ: SO I'LL OBJECT AS TO LACKS FOUNDATION AND AGAIN IS REDUNDANT. THIS IS EXACTLY THE TOPIC OF DR. RAPPAPORT'S TESTIMONY AND EXACTLY THE OPINION THAT DR. RAPPAPORT OFFERED. AND SO THIS IS CUMULATIVE AND REDUNDANT, UNDER 352.

THE COURT: OVERRULED.

MR. METZGER: ALL RIGHT.

Q PROFESSOR SMITH, IS ACRYLAMIDE CLASTOGENIC?

A YES.

Q AND HOW DO YOU KNOW THAT?

A WE KNOW THAT FROM VARIOUS STUDIES IN EXPERIMENTAL ANIMALS AND IN CELL CULTURES, WHERE ACRYLAMIDE PRODUCES CHROMOSOME BREAKS THAT CAN BE OBSERVED UNDER THE MICROSCOPE AND BY OTHER
METHODOLOGIES.

Q AND HOW IS ACRYLAMIDE CLASTOGENIC? CAN YOU EXPLAIN THAT.

A WELL, THERE ARE SEVERAL POSSIBILITIES. ACRYLAMIDE ITSELF IS NOT THAT REACTIVE WITH DNA. IT WILL REACT WITH DNA, BUT IT'S NOT AS REACTIVE AS ITS METABOLITE, GLYCIDAMIDE.

BUT ACRYLAMIDE DOES BIND TO THE CHROMATIN AND TO THE PROTEINS WHICH CONTROL THE STRUCTURE OF THE DNA. SO IT'S POSSIBLE THAT -- PROBABLE THAT THE ACRYLAMIDE BINDS THESE PROTEINS, AND THIS DISRUPTS THE NORMAL PROCESSES AND CAN LEAD TO BREAKS.

THE SECOND ALTERNATIVE IS THAT THE ACRYLAMIDE IS METABOLIZED BY CYTOCHROME P450 2E1 -- AND PERHAPS OTHER CYTOCHROMES -- TO GLYCIDAMIDE EPOXIDE, WHICH THEN REACTS WITH THE DNA AND CAUSES STRAND BREAKS IN THE DNA AND BREAKS THE CHROMOSOMES IN THAT WAY.

AND THE FINAL MECHANISM IS THAT ACRYLAMIDE ITSELF DIRECTLY BINDS TO AN ENZYME CALLED TOPOISOMERASE II, WHICH NORMALLY CONTROLS THE STRUCTURE OF THE DNA DURING CELL DIVISION.

AND SO THERE ARE AT LEAST THREE MECHANISMS, AND THEY PROBABLY ALL WORK TOGETHER IN CONCERT.

Q PROFESSOR SMITH, WOULD YOU TELL THE COURT WHAT YOUR CONCLUSIONS ARE REGARDING THE GENOTOXICITY OF ACRYLAMIDE.

A THAT ACRYLAMIDE IS CLEARLY GENOTOXIC. IT CLEARLY IS ABLE TO GET -- BE CONVERTED TO A METABOLITE
THAT BINDS TO DNA AND DAMAGES DNA, IS DNA REACTIVE. SO IT'S ABLE TO PRODUCE POINT MUTATIONS THROUGH ITS GLYCIDAMIDE.

THAT THE ACRYLAMIDE ITSELF WOULD BIND IMPORTANT PROTEINS ON THE DNA, ASSOCIATED WITH THE STRUCTURE OF DNA, THAT WILL ALTER THE FUNCTION OF DNA REPAIR AND THINGS LIKE THIS. AND SO THIS WILL LEAD TO CHROMOSOME BREAKS AND PERHAPS CHROMOSOME LOSS AND GAIN.

SO BASICALLY, ACRYLAMIDE IS CAPABLE OF CAUSING THE WHOLE SPECTRUM OF GENOTOXIC EFFECTS AND SHOULD BE CONSIDERED AS A GENOTOXIC CARCINOGEN THAT IS LINEAR TO LOW DOSES.

Q DR. RAPPAPORT TOLD THE COURT ABOUT THE DISTRIBUTION OF ACRYLAMIDE AND GLYCIDAMIDE TO THE TISSUES OF THE BODY, BUT I WOULD LIKE TO FOCUS WITH YOU ON ONE PARTICULAR ASPECT, WHICH IS: I'D LIKE YOU TO TELL THE COURT WHETHER ACRYLAMIDE IS DISTRIBUTED TO THE HUMAN FETUS.

A YES. THERE'S A VARIETY OF LINES OF EVIDENCE WHICH SHOW THAT ACRYLAMIDE WILL CROSS THE PLACENTA INTO THE FETUS.

THERE ARE STUDIES WHICH SHOW EFFECTS OF -- ON HUMANS, OF HIGH LEVELS OF DIETARY ACRYLAMIDE INTAKE LEADING TO LOWER FETAL GROWTH.

THERE ARE EFFECTS IN EXPERIMENTAL ANIMALS WHERE RADIO-LABELED ACRYLAMIDE HAS BEEN SHOWN TO CROSS INTO THE FETUS AND THAT THE LEVELS IN THE FETUS ARE VERY SIMILAR TO THE LEVELS IN THE BLOOD OF THE MOTHER.
SO THERE'S BEEN MEASUREMENTS OF ADDITION PRODUCTS -- CALLED ADDUCTS -- IN THE FETUS AND IN THE CORD BLOOD, COMPARED TO THE MOTHER; AND AGAIN, VERY SIMILAR LEVELS SHOWN.

SO THE PLACENTA DOESN'T FORM ANY SORT OF BARRIER TO ACRYLAMIDE CROSSING INTO THE FETUS.

Q DOES THE PLACENTA PROVIDE ANY PROTECTION TO THE TOXIC EFFECTS OF ACRYLAMIDE AND GLYCIDAMIDE?

A NO.

Q HOW DO YOU KNOW THAT?

A BECAUSE THE LEVELS ARE ABOUT THE SAME IN BOTH MATERNAL BLOOD AND THE BLOOD WHICH -- THE CORD BLOOD, WHICH SUPPLIES THE FETUS. SO THERE REALLY IS NO DIFFERENCE.

MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT AS A NEW AND UNDISCLOSED OPINION. THE SLIDE THAT HAS BEEN PUT UP BY MR. METZGER INCLUDES MATERIALS THAT WERE NOT PART OF DR. SMITH'S RELIANCE MATERIALS.

AND DR. SMITH DID NOT INDICATE THAT HE WAS GOING TO OFFER THESE OPINIONS DURING THE COURSE OF HIS DEPOSITION. AND THEREFORE, IT IS INAPPROPRIATE FOR HIM NOW TO BE OFFERING NEW AND UNDISCLOSED OPINIONS.

THE COURT: MR. METZGER?

MR. METZGER: MAY I LAY A FOUNDATION?

THE COURT: YES.

MR. METZGER: ALL RIGHT.

Q PROFESSOR SMITH, HAVE YOU READ THE EUROPEAN FOOD SAFETY AUTHORITY REPORT TITLED "DRAFT SCIENTIFIC
OPINION ON ACRYLAMIDE IN FOOD"?

A YES. IT WAS PUBLISHED IN JULY OF THIS YEAR.

Q WAS THAT AFTER YOU GAVE YOUR DEPOSITION IN THIS CASE?

A IT WAS.

Q OKAY. DOES THAT REPORT REINFORCE YOUR OPINION THAT THE PLACENTA PROVIDES NO PROTECTION TO THE FETUS?

MR. SCHURZ: WE'LL OBJECT. AND HE'S LAID A FOUNDATION THAT CLEARLY THE WITNESS DID NOT REVIEW THIS DOCUMENT --

THE COURT: OBJECTION SUSTAINED.

MR. METZGER: OKAY.

Q ALL RIGHT. PROFESSOR SMITH, DURING THIS TRIAL, THE TERM "SENSITIVE POPULATION" OR "SUBPOPULATION" CAME UP. ARE YOU FAMILIAR WITH THOSE TERMS?

A YES.

Q WHAT DO THEY MEAN?

A WELL, THEY MEAN THAT -- WHETHER A PERSON OR AN INDIVIDUAL COULD BE SENSITIVE IN VARIOUS WAYS, OR SUSCEPTIBLE, TO THE EFFECTS OF THE CHEMICAL. YOU COULD HAVE A CERTAIN GENETIC MAKEUP THAT MADE YOU SUSCEPTIBLE. YOU COULD BE VERY YOUNG OR VERY OLD, OR YOU COULD BE AN UNBORN CHILD. ALL OF THESE WOULD BE CONSIDERED TO BE SUSCEPTIBILITIES.

PREGNANT WOMEN ARE CLEARLY A POPULATION THAT'S CONSIDERED TO BE A SUSCEPTIBLE POPULATION.
Q: Why are unborn children susceptible populations?

A: Because they are developing. They are growing very quickly. Cells are dividing and changing. The fetus is clearly becoming a human being. And that process is very sensitive to interference by outside influences, such as toxic chemicals.

Q: Are infants also a sensitive population?

A: Infants are also a sensitive population because they're very small for the amount of air that they breathe in and the amount of food and water that they take in.

So clearly, the exposure of their tissues to a particular chemical could be much higher than that in an adult male, for example. And so, again, they're considered to be a sensitive population.

Q: Are sensitive populations, in your opinion, something that a risk assessor should consider?

A: Yes. They're well -- these factors are well understood by risk assessors, and there are guidelines to include additional safety factors if pregnant women or young children are exposed.

Q: Have you read publications of the World Health Organization regarding acrylamide?

A: I have. And the World Health Organization were one of the first to make comments about acrylamide, following its discovery in food in 2002.

Q: Do you agree with the conclusion of the
WORLD HEALTH ORGANIZATION THAT THE PRESENCE OF
ACRYLAMIDE IN FOOD IS A MAJOR CONCERN IN HUMANS, BASED
ON THE ABILITY TO INDUCE CANCER AND HERITABLE MUTATIONS
IN LABORATORY ANIMALS?

MR. SCHURZ: OBJECTION; HEARSAY. COUNSEL IS JUST
READING A DOCUMENT THAT'S NOT IN EVIDENCE.

THE COURT: OVERRULED.

THE WITNESS: YES. THE WORLD HEALTH ORGANIZATION
SAID THIS IN 2002, AND I BELIEVE IT'S STILL THEIR
POSITION. AND IT'S THE POSITION, CLEARLY, OF THE
EUROPEAN FOOD SAFETY AGENCY AND ALSO OF THE VARIOUS
UNITED STATES REGULATORY AGENCIES.

Q     BY MR. METZGER: DO YOU AGREE WITH THAT
POSITION?

A     I DO.

Q     WHY?

A     BECAUSE THE EVIDENCE IS OVERWHELMING THAT
ACRYLAMIDE IS CARCINOGENIC IN EXPERIMENTAL ANIMALS AND
THAT ITS MECHANISTIC -- OUR UNDERSTANDING OF ITS
MECHANISTIC CAPABILITIES IN PRODUCING CANCERS AND
GENETIC DAMAGE MAKE IT EXTREMELY LIKELY THAT IT'S A
HUMAN CARCINOGEN.

AND THIS MEANS THAT SINCE IT IS PRESENT IN
MANY FOODSTUFFS, THIS IS CLEARLY A MAJOR CONCERN, IF YOU
ARE INTERESTED IN PROTECTING PUBLIC HEALTH FROM
CARCINOGENIC RISK.

Q     ALL RIGHT. LET'S CHANGE TOPICS AND TALK
ABOUT COFFEE.
A OKAY.

Q HAVE YOU REVIEWED THE SCIENTIFIC LITERATURE REGARDING THE CLASTOGENIC NATURE OF COFFEE AND/OR ITS CONSTITUENTS?

A WELL, I AM FAMILIAR WITH THE FACT THAT COFFEE CONTAINS NUMEROUS CHEMICALS WHICH ARE KNOWN TO BE CLASTOGENIC, LARGELY THROUGH THEIR CONVERSION TO CAFFEIC ACID, WHICH IS A CLASTOGENIC COMPOUND;

AND ALSO, THAT IT CONTAINS METABOLITES OF BENZENE, HYDROQUINONE AND CATECHOL, THAT I KNOW FROM MY RESEARCH ON BENZENE.

MR. SCHURZ: AND YOUR HONOR, WE WOULD OBJECT TO THIS SLIDE, AS IT'S PROVIDED, IN THAT IT IDENTIFIES THREE ARTICLES THAT WERE NOT INCLUDED IN DR. SMITH'S RELIANCE MATERIALS AND ARE BEING SHOWN TO US HERE FOR THE FIRST TIME.

THE COURT: THE SLIDES ARE NOT IN EVIDENCE.

OBJECTION OVERRULED.

MR. METZGER: OKAY.

Q SO WOULD YOU TELL THE COURT ABOUT SOME OF THE CLASTOGENS THAT ARE PRESENT IN COFFEE.

A SO, FOR EXAMPLE, TWO METABOLITES OF BENZENE I'VE ALREADY MENTIONED, HYDROQUINONE AND CATECHOL, ARE PRESENT IN COFFEE.

COFFEE CONTAINS AT LEAST 6,000 CHEMICALS WHICH CAN BE IDENTIFIED. MANY OF THESE ARE PHENOLIC COMPOUNDS. THAT MEANS THEY HAVE OH GROUPS, OR HYDROXYL GROUPS, IN THEM. THESE CAN BE CONVERTED INTO REACTIVE
SPECIES WHICH CAN DAMAGE THE DNA.

THE OTHER TWO WELL-KNOWN ONES ARE
CHLOROGENIC ACID AND NEOCHLOROGENIC ACID, WHICH ARE
CONVERTED TO CAFFEIC ACID, WHICH IS ALSO PRESENT IN
COFFEE AND IS HIGHLY CLASTOGENIC.

SO THERE ARE -- AND THERE ARE ALSO A LIST OF
OTHER COMPOUNDS WHICH ARE COMMONLY FOUND IN PLANT
FOODSTUFFS, WHICH ARE FLAVENOIDS AND PHENOLS, WHICH ALSO
HAVE THIS PROPERTY.

Q OKAY. WHEN DID YOU FIRST BECOME AWARE THAT
SOME CHEMICALS IN COFFEE WERE CLASTOGENIC?

A WELL, ACTUALLY, THE FIRST TIME I REALLY
THOUGHT ABOUT THIS OR DISCUSSED THIS WITH ANYONE WAS
WITH BRUCE AMES, BACK IN THE LATE 1980S, WHEN HE WAS
EXAMINING THE EFFECTS OF CHEMICALS.

HE WROTE AN ARTICLE CALLED "PESTICIDES ARE
99.9 PERCENT NATURAL." AND IN THAT ARTICLE, IN THE
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, HE
BASICALLY DESCRIBED MANY OF THE CLASTOGENIC-TYPE
MOLECULES THAT WERE PRESENT IN VARIOUS FOODSTUFFS,
INCLUDING COFFEE.

AND BASICALLY, HE DESCRIBED HOW THESE POSE A
MORE SIGNIFICANT RISK, TYPICALLY, THAN MANY OF THE
POLLUTANTS, SUCH AS BENZENE -- INCLUDING BENZENE -- AT
VERY, VERY LOW DOSES.

SO HE AND I HAD A LOT OF DEBATES ABOUT THIS
TOPIC, AND IT'S WHEN I FIRST BECAME AWARE. IT WAS
PROBABLY IN 1986, OR SOMETHING LIKE THAT.
Q OKAY. YOU MENTIONED EARLIER HYDROQUINONE
AND CATECHOL, I BELIEVE, AS METABOLITES OF BENZENE.
A YES.
Q ARE THOSE CLASTOGENIC CHEMICALS?
A YES. IF YOU ADD THOSE TO CELLS, THEY BREAK
THE CHROMOSOMES OF THE CELLS.
Q AND ARE THOSE PRESENT IN COFFEE?
A YES.
Q I THINK YOU MENTIONED THAT BENZENE IS
METABOLIZED BY THE CYP2E1 ENZYME; IS THAT CORRECT?
A THAT'S CORRECT.
Q IS THAT THE SAME METABOLIC ENZYME BY WHICH
ACRYLAMIDE IS METABOLIZED TO GLYCIDAMIDE?
A IT IS.
Q AND WHAT IS THE SIGNIFICANCE OF THAT?
A WELL, THE SIGNIFICANCE IS THAT BASICALLY THE
SAME RISK FACTORS THAT -- AND THE SENSITIVITY FOR
BENZENE WILL APPLY TO ACRYLAMIDE ALSO.
Q OKAY. PROFESSOR SMITH, HAVE YOU AUTHORED
ARTICLES IN THE PEER-REVIEWED LITERATURE REGARDING THE
RELATIONSHIP BETWEEN CHEMICALS THAT AFFECT TOPOISOMERASE
II AND THE DEVELOPMENT OF LEUKEMIA?
A YES. SO ONE OF THE MECHANISMS BY WHICH
HYDROQUINONE AND CATECHOL AND OTHER METABOLITES OF
BENZENE ARE THOUGHT TO CAUSE LEUKEMIA IS THROUGH THE
INHIBITION OF TOPOISOMERASE II.
AND SO WE HAVE, SINCE THE MID 1990S, WITH MY
GRADUATE STUDENT DAVID EASTMAN -- WHO IS NOW A PROFESSOR
AT UC RIVERSIDE -- HAVE LOOKED AT THE ROLE OF
TOPOISOMERASE II INHIBITION AND LEUKEMIA INDUCED BY
BENZENE AND ITS METABOLITES.

Q AND YOU'VE PUBLISHED A NUMBER OF ARTICLES
ABOUT --

A YEAH, THIS IS JUST SOME OF THEM. THERE'S
QUITE A LOT THERE.

Q ALL RIGHT. WOULD YOU JUST TELL US WHAT YOU
HAVE CONCLUDED FROM YOUR OWN RESEARCH ON THIS TOPIC.

A THAT THE INHIBITION OF TOPOISOMERASE II CAN
OCUR IN HUMANS EXPOSED TO BENZENE. IT'S BEEN PROVEN BY
DAVID EASTMAN'S GROUP THAT IT OCCURS IN EXPERIMENTAL
ANIMALS, IN BONE MARROW, FOLLOWING EXPOSURE TO BENZENE;
AND THAT IT'S WIDELY CONSIDERED AND
GENERALLY ACCEPTED THAT INHIBITION OF TOPOISOMERASE II
IS A RISK FACTOR FOR FUTURE DEVELOPMENT OF LEUKEMIA.

THIS IS LARGELY KNOWN BECAUSE CANCER
CHEMOTHERAPY DRUGS, WHICH ARE USED TO TREAT BREAST
CANCER AND OTHER FORMS OF CANCER, LEAD TO LEUKEMIAS --
SECONDARY LEUKEMIAS IN THOSE CANCER PATIENTS AS A RESULT
OF THEM ACTING ON THE TOPOISOMERASE II IN THE BONE
Marrow.

Q HAVE YOU SELECTED A GRAPHIC WHICH DEPICTS
THE STRUCTURE OF TOPOISOMERASE II?

A YES.

Q IS THAT IT?

A WELL, THAT'S PART OF IT, ACTUALLY. IF YOU
TRY TO SHOW THE WHOLE OF IT, IT BECOMES VERY
COMPLICATED.

THIS IS ACTUALLY THE DI/MO, WHICH IS WHAT'S CALLED A TERMINAL ATPA. IT'S VERY TECHNICAL WORDS. AND IT'S A DI/MO BECAUSE IT'S TWO TYPES OF PROTEIN BOUND TOGETHER THERE, WHICH IS LIKE A MIRROR TO EACH OTHER.

WHEN THEY COME TOGETHER, YOU CAN SEE THAT THERE'S LIKE A HEART SHAPE, UPSIDE-DOWN HEART SHAPE, AT THE BOTTOM. ONE STRAND OF DNA GOES IN THERE. THAT'S CALLED THE T DOMAIN. AND THERE'S ONE GATE IN THE PROTEIN.

AND AT THE TOP, THE DNA IS THREADED THROUGH -- THE OTHER STRAND OF DNA IS THREADED THROUGH THE TOP OF THE ENZYME IN AN ANGLE OF ABOUT 160 DEGREES AND BENT THROUGH THAT TOP GATE. AND THAT'S CALLED THE END GATE.

AND THAT THEN BRINGS THE TWO STRANDS OF THE DNA INTO ALIGNMENT, OR UNTANGLING.

Q UNTANGLING?

A YES.

Q ALL RIGHT. SO WHAT DOES TOPOISOMERASE II -- THAT ENZYME, WHAT DOES IT DO?

A IT'S THERE IN YOUR CELLS. IT'S THERE IN EVERY CELL, FROM BACTERIA ONWARDS. AND ITS ROLE IS THAT -- WHEN CELLS ARE NOT DIVIDING, YOUR DNA IS ALL WOUND UP AND PACKAGED LIKE A BALL OF STRING OR A BALL OF WOOL. SO IT HAS TO BE UNTANGLED AND PULLED OUT AS A SINGLE STRING IN ORDER FOR IT TO BE COPIED.

AND SO WHAT THE TOPOISOMERASE DOES IS JUST
BASICALLY MAKES SURE THAT THE DNA DOESN'T GET TANGLED AS
YOU UNTANGLE THE BALL OF WOOL. THAT'S WHY EVERY CELL,
FROM BACTERIA ON, HAS IT.

Q OKAY. I BELIEVE YOU'VE SELECTED SOME
GRAPHICS TO SHOW WHAT TOPOISOMERASE II DOES. LET'S TAKE
A LOOK AT THE NEXT ONE, IF WE COULD.

DO WE NOT HAVE THE GRAPHIC? IT'S NOT
SHOWING. WELL --

A IF YOU GO BACK TO THE PREVIOUS SLIDE, I CAN
EXPLAIN.

Q ALL RIGHT. LET'S GO BACK TO THE PREVIOUS
SLIDE.

A SO AS I MENTIONED, ONE STRAND OF THE DNA
GOES THROUGH THE HEART SHAPE -- UPSIDE-DOWN HEART SHAPE
AT THE BOTTOM. THE SECOND STRAND COMES IN AT THE TOP
AND FEEDS THROUGH THERE, LOOPS THROUGH THERE.

IT'S THEN -- RIGHT IN THE MIDDLE OF THE TOP
THERE, YOU CAN SEE THERE'S LIKE A -- ALMOST LIKE A
SCISSOR DEVICE. THAT CUTS THE DNA.

THE TWO STRANDS THEN -- THIS THEN ALLOWS YOU
TO EITHER UNHOOK OR UNLOOP THE STRAND THAT'S GOING
THROUGH THE BOTTOM, OR TO LOOP IT THROUGH. AND THEN YOU
CAN RESEAL IT AT THE TOP, AND YOU CAN UNTANGLE THE DNA
IN THAT FASHION.

SO YOU CUT AND REJOIN WITHIN THE ENZYME.

Q OKAY.

A THIS ALSO MEANS THAT IF YOU INHIBIT THE
ENZYME OR DAMAGE IT IN SOME WAY, THAT THAT BREAK COULD
Q: OKAY. I THINK WE DO HAVE A GRAPHIC WHICH SHOWS -- WELL, TELL US -- EXPLAIN TO THE COURT WHAT THIS SHOWS.

A: SO IN THIS WAY, AS I JUST MENTIONED, YOU COULD FEED THE TOP LOOP THROUGH THE -- ONE LOOP COULD GO THROUGH THE TOP PART OF THE PROTEIN AND THE OTHER LOOP THROUGH THE BOTTOM. YOU COULD CUT ONE, AND THEN YOU COULD SEPARATE THEM OUT.

YOU CAN UNWIND -- YOU CAN TWIST THE PROTEIN AROUND SO THAT IT WILL UNWIND THE DNA. AND YOU CAN ALSO TAKE OUT KNOTS BY CUTTING AND REJOINING.

SO IT'S JUST LIKE HAVING A TWISTED-UP ROPE. YOU COULD CUT IT AND THEN JOIN IT BACK TOGETHER AND THEN HAVE IT BE STRAIGHT.

Q: AND THIS ONE ENZYME DOES ALL THOSE THINGS?

A: THIS ONE ENZYME DOES ALL THOSE THINGS, AND IT'S AN ABSOLUTELY CRITICAL ENZYME IN LIFE. AND IT'S ALSO THE TARGET IN BACTERIA FOR MOST OF THE ANTIBIOTICS WE TAKE.

Q: DO SOME OF THE CLASTOGENIC CHEMICALS IN COFFEE INHIBIT THE ABILITY OF TOPOISOMERASE II TO REPAIR TANGLED DNA?

A: YES. ACRYLAMIDE WILL INHIBIT TOPOISOMERASE II. AND SO WILL SOME OF THE OTHER -- SUCH AS CHLOROGENIC ACID, THAT I MENTIONED EARLIER, AND HYDROXYHYDROQUINONE, WHICH ARE PRESENT IN COFFEE -- WILL...
ALSO DAMAGE TOPOISOMERASE II AND INHIBIT ITS NORMAL ACTIVITY.

Q ALL RIGHT. PROFESSOR SMITH, HAVE YOU PUBLISHED REGARDING CHILDHOOD LEUKEMIA?

A I HAVE.

Q APPROXIMATELY HOW MANY ARTICLES?

A COULD I ASK YOU, MR. METZGER, BEFORE WE GO ON TO CHILDHOOD LEUKEMIA, COULD I TAKE A SHORT BATHROOM BREAK?

MR. METZGER: YOUR HONOR, MAY WE?

THE COURT: YES. WE'LL TAKE A TEN-MINUTE RECESS AT THIS TIME.

(RECESS.)

THE COURT: BACK ON THE RECORD IN CERT VS. STARBUCKS. PLEASE BE SEATED.

PROFESSOR SMITH IS ON THE STAND.

PROFESSOR SMITH, YOU UNDERSTAND YOU'RE STILL UNDER OATH?

THE WITNESS: I DO.

THE COURT: PLEASE STATE YOUR NAME FOR THE RECORD.

THE WITNESS: MY NAME IS MARTYN THOMAS SMITH.

THE COURT: THANK YOU.

MR. METZGER IS INQUIRING.

MR. METZGER: THANK YOU, YOUR HONOR.

THE COURT: COUNSEL, YOU MAY PROCEED.

Q BY MR. METZGER: PROFESSOR SMITH, BEFORE THE BREAK, WE WERE -- YOU WERE TELLING THE COURT ABOUT TOPOISOMERASE INHIBITORS AND LEUKEMIA.
WOULD YOU EXPLAIN TO THE COURT WHAT CHEMICAL TOPOISOMERASE INHIBITORS HAVE BEEN SHOWN TO BE INVOLVED IN THE DEVELOPMENT OF LEUKEMIA, AND EXPLAIN WHY.

A SO AS I MENTIONED, SEVERAL CHEMICALS WHICH I'VE USED TO TREAT CANCER HAVE THE UNFORTUNATE ABILITY TO INHIBIT TOPOISOMERASE II AND THEREBY GENERATE LEUKEMIA IN SOME OF THE PATIENTS WHO I'VE TREATED.

Q SO --

A AND --

Q LET ME SEE IF I UNDERSTAND. THERE ARE PATIENTS WHO HAVE CANCER -- NOT NECESSARILY LEUKEMIA, BUT OTHER CANCERS --

A CORRECT.

Q -- AND THEY'RE TREATED WITH CERTAIN DRUGS THAT ARE, WHAT?

A THEY ARE -- THEY ARE DNA-REACTIVE-TYPE COMPOUNDS. THE CLASS OF COMPOUNDS WHICH ARE BEST KNOWN TO INHIBIT TOPOISOMERASE II ARE CALLED PODOPHYLLOTOXINS, AND THEY'RE USED TO TREAT LYMPHOMA, BREAST CANCER. AND ANOTHER VERY COMMON ONE IS ADRIAMYCIN.

Q AND WHAT DO THESE CHEMOTHERAPY DRUGS HAVE IN COMMON, THAT YOU'RE TALKING ABOUT HERE?

A THEY ALL DAMAGE THE DNA OF CANCER CELLS AND KILL THE CANCER CELLS; BUT THEY HAVE THE SECONDARY EFFECT OF INHIBITING THE TOPOISOMERASE II IN THE BONE MARROW STEM CELLS, WHICH LEADS TO -- IN SOME PATIENTS, TO SECONDARY LEUKEMIA.

Q WHAT IS A SECONDARY LEUKEMIA?
A IT'S A LEUKEMIA ARISING AFTER ANOTHER CANCER, SO SECONDARY TO TREATMENT WITH A CANCER DRUG.

Q IN THIS CASE, A DRUG THAT DAMAGES THE TOPOISOMERASE II ENZYME?

A CORRECT.

Q OKAY. AND WHAT IS SUCH A DRUG?

A SO DRUGS -- ETOPOSIDE IS ONE OF THEM; ADRIAMYCIN, MITOXANTRONE.

THIS IS ACTUALLY A MAJOR ISSUE IN CLINIC BECAUSE 10 PERCENT OF THE LEUKEMIAS CAUSED IN THE UNITED STATES ARE ACTUALLY CAUSED BY CANCER TREATMENT FOR OTHER CANCERS, AND THIS IS LARGELY THE MECHANISM THROUGH TOPOISOMERASE II INHIBITION.

Q OKAY. NOW, HAVE CHEMICALS THAT INHIBIT THE TOPOISOMERASE II ENZYME ALSO BEEN INVOLVED IN THE DEVELOPMENT OF CHILDHOOD LEUKEMIA?

A YES. SO AWARENESS OF THIS CONCEPT THAT CHEMICALS USED TO TREAT CANCER WOULD INHIBIT TOPOISOMERASE II AND LEAD TO SECONDARY CANCERS IN THOSE PATIENTS RAISED AWARENESS THAT THERE MAY BE OTHER TOPOISOMERASE II IN OUR ENVIRONMENT -- OR CHEMICALS WHICH WOULD INHIBIT IT, EITHER IN OUR FOOD OR WATER OR AIR, THAT WOULD ALSO ACT AS TOPOISOMERASE II INHIBITORS AND COULD CAUSE BOTH ADULT LEUKEMIA AND ALSO CHILDHOOD LEUKEMIA.

SO THE FIRST SUGGESTION OF THIS CAME FROM JULIE ROSS'S WORK, WHERE SHE STUDIED POTENTIAL INTAKE OF TOPOISOMERASE II INHIBITORS FROM DIET AND ITS...
ASSOCIATION WITH AN EARLY FORM OF CHILDHOOD LEUKEMIA CALLED INFANT LEUKEMIA, WHICH OCCURS WITHIN THE FIRST YEAR OR TWO OF LIFE.

Q OKAY. AND TELL US ABOUT THE STUDIES IN THIS AREA THAT FOLLOWED DR. ROSS'S STUDY THAT ARE SIGNIFICANT TO YOU.

A SO THE WAY THAT -- INFANT LEUKEMIA HAS A VERY PARTICULAR CHROMOSOME CHANGE IN IT. IT INVOLVES PART OF CHROMOSOME 11, AND IT'S WHERE WHAT'S CALLED THE MLL GENE IS LOCATED.

IT WAS FOUND VERY EARLY ON THAT IDENTICAL TWINS COULD BE BORN WITH LEUKEMIA, AS A CHANGE -- BECAUSE OF THE CHANGE IN THIS MLL GENE, SHOWING THAT IT AROSE IN UTERO.

IT WAS THEN FOUND THAT YOU COULD DETECT THIS MUTATION IN THE BLOOD SPOTS TAKEN AT BIRTH, BEFORE THE CHILD DEVELOPED LEUKEMIA.

AND IN OUR STUDY IN NORTHERN CALIFORNIA, SIX CHILDREN WERE ACTUALLY BORN WITH LEUKEMIA, WITH THIS TRANSLOCATION AT 11Q ON CHROMOSOME 11.

SO PEOPLE BEGAN TO BE INTERESTED IN WHAT WOULD BREAK THIS REGION OF THE CHROMOSOME.

Q CHROMOSOME 11?

A CHROMOSOME 11.

AND SO PEOPLE EXPOSED CELLS IN CULTURE TO VARIOUS CHEMICALS WHICH THEY THOUGHT WOULD BE TOPOISOMERASE II INHIBITORS, INCLUDING SOME CHEMICALS FOUND IN SOY AND -- OTHER CHEMICALS FOUND IN SOY, SUCH
AS GENISTEIN, G-E-N-I-S-T-E-I-N, THAT WOULD DAMAGE THIS PARTICULAR AREA OF CHROMOSOME 11.

AND IT WAS FOUND BY COLLEAGUES IN CHICAGO THAT THERE WERE A WHOLE VARIETY OF CHEMICALS WHICH WOULD BREAK CHROMOSOME 11 AT THIS POSITION, WHICH SUPPORTED THE HYPOTHESIS THAT THESE CHEMICALS WITHIN THE DIET AND WITHIN OUR FOOD WOULD CAUSE CHILDHOOD LEUKEMIA.

A SUBSEQUENT LARGER STUDY WITHIN THE CHILDREN'S ONCOLOGY GROUP, BY SPECTOR AND OTHERS, BASICALLY CONFIRMED THIS HYPOTHESIS: THAT FOR A SPECIFIC TYPE OF LEUKEMIA, THROUGH THE CHANGE IN THE MLL GENE, THE HIGH INTAKE OF THOSE TOPOISOMERASE II INHIBITORS WOULD CAUSE THAT TYPE OF INFANT LEUKEMIA.

Q ALL RIGHT. THANK YOU.

SO HAVE YOU IN THIS CASE FORMED AN OPINION AS TO WHETHER CLASTOGENIC CHEMICALS IN COFFEE PRESENT A RISK OF CHILDHOOD LEUKEMIA?

A YES.

Q AND WHAT IS YOUR OPINION?

A MY OPINION IS THAT THERE ARE STUDIES WHICH FIND AN ASSOCIATION BETWEEN HIGH INTAKE OF COFFEE AND CHILDHOOD LEUKEMIA RISK.

AND THE MOST PROBABLE MECHANISM TO EXPLAIN THIS IS THAT THE CLASTOGENIC CHEMICALS WITHIN COFFEE, INCLUDING ACRYLAMIDE, CROSS INTO THE FETUS AND CAUSE GENETIC DAMAGE IN THE FETUS OF THE TYPE WHERE THERE'S CHROMOSOME BREAKAGE, WHICH LEADS TO CHROMOSOME TRANSLOCATIONS, WHICH THEN DEVELOPS INTO LEUKEMIA.
Q INTO CHILDHOOD LEUKEMIA?
A CORRECT.
Q OKAY. LET'S FIRST -- BEFORE WE GET INTO THE SPECIFICS OF THAT, I'D LIKE TO REVIEW SOME OF YOUR OWN RESEARCH PUBLICATIONS REGARDING CHROMOSOME DAMAGE AND CHILDHOOD LEUKEMIA.

LET ME JUST ASK YOU: IS ONE OF THE ARTICLES THAT YOU AUTHORED AN ARTICLE TITLED "PRENATAL ORIGIN OF CHILDHOOD ACUTE MYELOID LEUKEMIAS HARBORING CHROMOSOMAL REARRANGEMENTS T(15; 17) AND INVERSION(16)?
A YES.
Q AND WOULD YOU TELL THE COURT WHAT YOU DID IN THAT STUDY AND WHAT YOU CONCLUDED.
A OKAY. SO WE HAVE COLLECTED, WITH PATRICIA BUFFLER, MORE THAN 1,000 CASES OF CHILDHOOD LEUKEMIA IN NORTHERN CALIFORNIA, AND WE HAVE CHARACTERIZED THE CHROMOSOME CHANGES THAT ARE PRESENT WITHIN THEM.

SO THE OTHER FORTUNATE THING FOR US, AS RESEARCHERS IN CALIFORNIA, IS THAT SINCE 1966, EVERY BABY AT BIRTH HAS HAD A BLOOD SPOT STORED IN A FILING CABINET IN SACRAMENTO, WHERE SPOTS OF BLOOD ARE PUT ON WHAT'S CALLED A GUTHRIE CARD AND STORED THERE.

NOW, WITH SPECIAL PERMISSION, YOU CAN REQUEST THESE BLOOD CARDS FROM THE STATE. SO FOR THIS REASON, WE WERE ABLE TO IDENTIFY A SERIES OF CHILDHOOD LEUKEMIA PATIENTS IN CALIFORNIA WHO HAD THESE PARTICULAR CHROMOSOME CHANGES: THE TRANSLOCATION BETWEEN CHROMOSOME 15 AND 17 AND AN INVERSION OF CHROMOSOME 16,
WHERE PART OF THE CHROMOSOME IS SPUN AROUND.

SO WHAT WE WANTED TO DO IS TO TRY TO DETECT THESE CHROMOSOME CHANGES IN THE BLOOD SPOT TAKEN AT BIRTH AND STORED IN SACRAMENTO.

Q WHAT WAS THE PURPOSE OF THAT?
A SO WE COULD THEN SEE WHETHER THE DISEASE WAS PRESENT AT BIRTH.

Q OKAY.
A AND SO WHAT WE FOUND WAS, THE DISEASE WAS PRESENT AT BIRTH IN MOST OF THESE CASES. AND FOR ALMOST EVERYTHING WE'VE LOOKED AT, WITH ONE EXCEPTION, THE CHROMOSOME CHANGES THAT ARE PRESENT IN THE LEUKEMIA ARE PRESENT AT BIRTH.

THE IMPORTANT PART ABOUT THIS IS THAT EACH PATIENT HAS THEIR OWN UNIQUE CHROMOSOME CHANGE. SO YOU CAN DETECT THAT UNIQUE CHROMOSOME CHANGE IN THEIR OWN BLOOD AT BIRTH, WHICH SHOWS THAT THE DISEASE WAS THERE BEFORE THEY WERE BORN.

AS THEY GROW, OF COURSE, WHAT HAPPENS IS, THE LEUKEMIC CELLS GROW AND DIVIDE AND POPULATE THE BLOOD, AND CHILDHOOD LEUKEMIA DEVELOPS.

Q OKAY.
A SO IT BEGINS WITHIN THE FETUS.

Q AS CHROMOSOME DAMAGE?
A AS CHROMOSOME DAMAGE.

Q OKAY. ANOTHER ARTICLE THAT YOU AND YOUR COLLEAGUES WROTE IS TITLED "PRENATAL ORIGIN OF CHROMOSOMAL TRANSLocations IN ACUTE CHILDHOOD LEUKEMIA:
IMPLICATIONS AND FUTURE DIRECTIONS."

WILL YOU TELL THE

COURT WHAT THAT ARTICLE IS ABOUT.

A WELL, THAT ARTICLE BASICALLY USED THE

FINDINGS THAT WERE MOSTLY FROM OUR GROUP IN CALIFORNIA

AND A GROUP IN LONDON LED BY MEL GREAVES, WHICH

BASICALLY IDENTIFIED A WHOLE SERIES OF CHROMOSOMAL

CHANGES WHICH WOULD OCCUR BEFORE A CHILD IS BORN WHICH

COULD LEAD TO CHILDHOOD LEUKEMIA.

ONE OF THE ISSUES WITH THIS WAS THEN, WELL,

CAN YOU THEN PREDICT WHO IS GOING TO GET CHILDHOOD

LEUKEMIA BY A TEST AT BIRTH?

AND THE PROBLEM WITH THAT IS THAT THESE

CHROMOSOME CHANGES ARE PRESENT IN A LARGE NUMBER OF

CHILDREN, ONLY 1 PERCENT OF WHICH WILL GO ON TO DEVELOP

LEUKEMIA.

AND SO IT'S NOT A GOOD ENOUGH TEST IN TERMS

OF PREDICTION OF WHO WILL GET LEUKEMIA, BUT IT DOES SHOW

THAT -- FOR A PARTICULAR PATIENT, WHEN THEIR LEUKEMIA

BEGAN.

Q OKAY. YOU ALSO HAVE AN ARTICLE TITLED

"MOLECULAR BIOMARKERS FOR THE STUDY OF CHILDHOOD

LEUKEMIA." TELL THE COURT WHAT THAT'S ABOUT.

A THAT, AGAIN, IS ABOUT A REVIEW OF THIS TYPE

OF ISSUE AND ALSO ABOUT SOME OF THE WORK WE DID LOOKING

FOR PEOPLE WHO WOULD BE SUSCEPTIBLE -- GENETICALLY

SUSCEPTIBLE TO CHILDHOOD LEUKEMIA.

Q PROFESSOR SMITH, HAVE YOU FORMED AN OPINION

AS TO WHETHER IT IS GENERALLY ACCEPTED IN THE SCIENTIFIC
COMMUNITY THAT CHILDHOOD LEUKEMIA DEVELOPS IN UTERO FROM CHROMOSOMAL CHANGES IN THE FETUS WHICH LEAD TO THE -- EVENTUALLY, TO THE DEVELOPMENT OF LEUKEMIA IN INFANTS AND CHILDREN?

MR. SCHURZ: OBJECTION; LACKS FOUNDATION AS TO THIS WITNESS’S KNOWLEDGE AND ABILITY TO SPEAK ON BEHALF OF STANDARDS GENERALLY ACCEPTED IN THE SCIENTIFIC COMMUNITY.

THE COURT: MR. METZGER, LAY A FOUNDATION.

Q BY MR. METZGER: PROFESSOR SMITH, HAVE YOU -- DO YOU FREQUENTLY ATTEND SCIENTIFIC MEETINGS OF EXPERTS IN CHILDHOOD LEUKEMOGENESIS?

A I DO.

Q WOULD YOU TELL US ABOUT THOSE.

A WELL, FOR EXAMPLE, THERE’S AN INTERNATIONAL CONSORTIUM OF STUDIES OF COHORTS OF CHILDREN IN THE WORLD WHICH MEETS REGULARLY, THAT I AM COLLABORATING WITH TO TRY AND DEVELOP MARKERS IN THE BLOOD WHICH WOULD PREDICT CHILDHOOD LEUKEMIA AND FIND ITS CAUSES.

I AM, IN CONNECTION WITH A LARGE NUMBER OF RESEARCHERS THROUGHOUT THE WORLD, DOING A STUDY OF CHILDHOOD LEUKEMIA.

AND FOR EXAMPLE, I RECENTLY PARTICIPATED AS AN INVITED DISCUSSANT AND PRESENTER OF A WEBINAR PRODUCED BY THE CENTERS FOR DISEASE CONTROL, WITH THE AIM OF LOOKING AT WAYS TO PREVENT CHILDHOOD CANCER, WHERE I SPOKE ABOUT BENZENE AS A CAUSE OF CHILDHOOD CANCER.
AND I AM IN REGULAR TOUCH WITH ALL THE LEADING RESEARCHERS IN THE WORLD ON THIS TOPIC.

Q OKAY. AND HOW LONG HAVE YOU BEEN IN TOUCH WITH THE LEADING RESEARCHERS IN THE WORLD REGARDING THE PATHOGENESIS OF CHILDHOOD LEUKEMIA?

A SINCE WE DESIGNED THE STUDY AND BEGAN IT IN THE EARLY 1990S.

Q OKAY. AS A RESULT OF YOUR PARTICIPATION IN THESE MEETINGS OF CHILDHOOD LEUKEMIA EXPERTS THROUGHOUT THE WORLD AND YOUR RESEARCH IN THE FIELD, HAVE YOU COME TO HAVE AN UNDERSTANDING AS TO WHETHER THERE IS GENERAL ACCEPTANCE IN THIS SCIENTIFIC COMMUNITY THAT CHILDHOOD LEUKEMIA DEVELOPS IN UTERO FROM CHROMOSOMAL CHANGES IN THE FETUS?

MR. SCHURZ: OBJECTION; LACKS FOUNDATION AS TO THIS WITNESS'S UNDERSTANDING AS TO WHAT IS THE GENERAL ACCEPTANCE WITHIN THE SCIENTIFIC COMMUNITY.

ALL WE'VE HEARD IS UNNAMED EXPERTS THROUGHOUT THE WORLD AND DR. SMITH'S OWN RESEARCH. WE'VE HEARD NOTHING WITH RESPECT TO RECOGNIZED GOVERNMENT REGULATORY ASSOCIATIONS ADOPTING THIS VIEW. LACKS FOUNDATION.

THE COURT: OVERRULED.

THE WITNESS MAY ANSWER THE QUESTION.

THE WITNESS: THE GENERAL CONSENSUS IN THE SCIENTIFIC COMMUNITY IS THAT CHROMOSOME CHANGES ARISING IN UTERO ARE A MAJOR CAUSE OF CHILDHOOD LEUKEMIA; AND THAT THERE ARE EXCEPTIONS, BUT IN GENERAL, MOST
CHILDHOOD LEUKEMIAS OCCUR -- ARISE FROM A PROCESS THAT BEGINS IN THE FETUS.

Q BY MR. METZGER: ALL RIGHT. HAVE YOU FORMED AN OPINION AS TO WHETHER DNA IN THE HUMAN FETUS CAN BE EXPOSED TO CLASTOGENS IN COFFEE?

A YES, BECAUSE THE BARRIER -- THE SUPPOSED PLACENTAL BARRIER ISN'T REALLY A BARRIER AT ALL. IT'S A BARRIER TO INFECTIOUS AGENTS AND THINGS LIKE THIS, BUT IT'S NOT A BARRIER TO THESE SMALL MOLECULES, CHEMICALS FOUND IN COFFEE OR ACRYLAMIDE OR THESE THINGS. THESE PASS READILY INTO THE FETUS AND COULD INTERACT WITH THE DNA THERE.

Q HAVE YOU FORMED AN OPINION AS TO HOW CLASTOGENS IN COFFEE CAN DAMAGE FETAL DNA IN BONE MARROW CELLS?

A THEY CAN -- AS I'VE JUST MENTIONED, THEY COULD GET INTO THE BLOODSTREAM OF THE MOTHER. THEY COULD BE ACTIVATED BY CYTOCHROME P450 2E1, IF NECESSARY, OR CONVERTED IN THE MOTHER TO TOXIC METABOLITES, WHICH WOULD THEN TRAVEL INTO THE FETUS.

ALL THESE PURE COMPOUNDS CAN TRAVEL INTO THE FETUS IN A BASICALLY UNINHIBITED WAY AND REACH THE DEVELOPING BLOOD OF THE FETUS, WHICH CAN BE IN THE LIVER IN EARLY LIFE AND IN THE BONE MARROW AT -- MOSTLY IN THE BONE MARROW AT FIVE MONTHS OF GESTATION.

SO THIS WAY, THE STEM CELLS COULD BE DAMAGED, ARISING TO PRODUCE LEUKEMIA.

Q ALL RIGHT. WHEN YOU SAY THIS COULD OCCUR,
IS THERE EVIDENCE THAT IT DOES OCCUR?

A. THERE IS EVIDENCE THAT DRINKING HIGH AMOUNTS
OF COFFEE DURING PREGNANCY IS ASSOCIATED WITH AN
INCREASED RISK OF CHILDHOOD LEUKEMIA.

Q. AND WHAT IS THAT EVIDENCE?

A. THAT EVIDENCE BEGAN, REALLY, OUT OF THE ROSS
STUDIES -- AGAIN, THAT I MENTIONED -- WHICH GOT THIS
FIELD GOING ABOUT TOPOISOMERASE II INHIBITORS.

ONE OF THE THINGS SHE CONSIDERED IN HER
STUDY WAS COFFEE. PEOPLE THEN FOLLOWED THAT UP; MOST
NOTABLY, THESE FRENCH RESEARCHERS, WHICH DID A STUDY IN
PARIS OF CASES AND CONTROLS AND LOOKED AT COFFEE
CONSUMPTION OF THE MOTHER.

AND THEY FOUND THAT FOR A HIGH INTAKE OF
COFFEE, THERE WAS AN INCREASED RISK OF CHILDHOOD
LEUKEMIA.

SUBSEQUENTLY, ANOTHER STUDY BY THE SAME
GROUP IN A DIFFERENT POPULATION FOUND SAME THING. THERE
WAS A SUGGESTION IN AN AUSTRALIAN STUDY OF A SIMILAR
FINDING, BUT IT DIDN'T -- IT WASN'T QUITE STATISTICALLY
SIGNIFICANT.

AND THEN IN A MUCH LARGER FRENCH NATIONWIDE
STUDY -- RECENTLY PUBLISHED, IN 2013 -- THIS WAS AGAIN
CONFIRMED: THAT WITH A HIGH INTAKE OF COFFEE, THERE WAS
AN INCREASED RISK OF CHILDHOOD LEUKEMIA.

AND SUBSEQUENTLY, A META-ANALYSIS OF ALL OF
THOSE STUDIES CONCLUDED THAT THERE WAS AN ASSOCIATION
BETWEEN HIGH INTAKE OF COFFEE AND SUBSEQUENT RISK OF
CHILDHOOD LEUKEMIA. AND THE INVESTIGATORS CALLED FOR FURTHER STUDY OF THIS IN LARGE INTERNATIONAL COHORTS.

MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT AND MOVE TO STRIKE UNDER 352 AS REDUNDANT.

ALL OF THE STUDIES THAT DR. SMITH JUST REFERENCED WERE DISCUSSED AT SOME LENGTH BY DR. MELNICK. SO WE'VE NOW HEARD FROM TWO EXPERTS WITH RESPECT TO THE SAME SET OF STUDIES AND THEIR ANALYSIS OF THOSE STUDIES. I SUSPECT THAT WE'RE GOING TO HEAR FROM YET ANOTHER IN THE FORM OF DR. PETER INFANTE. SO WE WOULD MOVE TO STRIKE DR. SMITH'S TESTIMONY AS REDUNDANT AND DUPLICATIVE, UNDER 352.

THE COURT: THE OBJECTION IS OVERRULED. NEXT QUESTION.

Q BY MR. METZGER: OKAY. PROFESSOR SMITH, HAVE YOU FORMED AN OPINION AS TO WHETHER EXPOSURE TO THE FETUS -- EXPOSURE OF THE FETUS TO CLASTOGENS FROM MATERNAL CONSUMPTION OF COFFEE DURING PREGNANCY IS A BIOLOGICALLY PLAUSIBLE MECHANISM FOR THE DEVELOPMENT OF CHILDHOOD LEUKEMIA?

A YES, I HAVE.

ONE OF THE FACTORS ONE MUST CONSIDER IN LOOKING AT WHETHER SOMETHING CAUSES A PARTICULAR DISEASE IS BIOLOGICAL PLAUSIBILITY.

AND THE IDEA THAT CHEMICALS FROM COFFEE COULD CROSS THE PLACENTA INTO THE FETUS AND PRODUCE CHROMOSOME DAMAGE OF THE TYPE FOUND IN CHILDHOOD LEUKEMIA ADDS WEIGHT TO THE CONCEPT THAT COFFEE -- HIGH
INTAKE OF COFFEE CAN PRODUCE CHILDHOOD LEUKEMIA, BECAUSE
OF IT BEING BIOLOGICALLY PLAUSIBLE.

Q WHAT IS IT ABOUT THE BIOLOGICAL PLAUABILITY
OF, SPECIFICALLY, CLASTOGENS IN COFFEE THAT IS
BIOLOGICALLY PLAUSIBLE?

A WELL, IT'S BECAUSE, AS I'VE MENTIONED, THESE
CHROMOSOME CHANGES OCCUR BEFORE BIRTH. AND THESE
CHROMOSOME CHANGES ARE STRUCTURAL REARRANGEMENTS, WHERE
ONE CHROMOSOME IS FUSED WITH ANOTHER, OR PART OF IT IS
TWISTED AROUND. AND THIS IS -- WILL BE PRODUCED -- THIS
WOULD BE AN EFFECT PRODUCED BY A CLASTOGEN.

SO THE CLASTOGEN PRODUCES THE CHROMOSOME
CHANGES OF THE TYPE FOUND IN CHILDHOOD LEUKEMIA, WHICH
OCCURS BEFORE BIRTH. IT CAN BE DETECTED IN THE BLOOD
SPOT THAT WAS TAKEN AT BIRTH AND, SUBSEQUENTLY, IN THE
PATIENTS WHERE LEUKEMIA DEVELOPS IN THE POPULATION.

Q OKAY. AND EARLIER, YOU MENTIONED
EPIDEMIOLOGIC STUDIES OF PEOPLE WHO WERE FOLLOWED -- I
THINK, IN SWEDEN -- TO SEE IF THEY DEVELOPED LEUKEMIA OR
CANCERS IN RELATIONSHIP TO THE CHROMOSOMAL ABNORMALITIES
THAT THEY HAD.

DOES THAT -- DO THOSE STUDIES SUPPORT YOUR
OPINION?

A WELL, THEY DO.

MR. SCHURZ: OBJECTION; LEADING.

THE COURT: SUSTAINED.

Q BY MR. METZGER: WOULD YOU TELL THE COURT,
WHAT ABOUT THOSE STUDIES IS SIGNIFICANT TO YOU IN YOUR
ASSESSMENT OF THIS ISSUE?

A  SO CLASTOGENS PRODUCE STRUCTURAL CHROMOSOMAL
ABERRATIONS OF THE TYPE THAT HAVE BEEN SHOWN TO BE
PREDICTIVE OF FUTURE CANCER RISK. AND THIS IS AN
EXAMPLE IN ADULTS, BUT THEY ALSO APPLY IN THIS CASE TO
THE DEVELOPMENT OF CHILDHOOD CANCER IN CHILDREN.

Q  OKAY. LET ME ASK YOU: WHEN YOU SAY
"PREDICTIVE OF FUTURE CANCER RISK," HOW MANY DIFFERENT
THINGS HAVE ACTUALLY BEEN SHOWN, IN MEDICAL SCIENCE, TO
BE PREDICTIVE OF FUTURE CANCER RISK?

A  ONLY TWO THINGS: CHROMOSOME ABERRATIONS AND
MICRONUCLEI; NOTHING ELSE.

Q  OKAY.

A  IT'S ONE OF THE BIG RESEARCH QUESTIONS OF
THE DAY.

Q  AND DOES ACRYLAMIDE, WHEN METABOLIZED TO
GLYCIDAMIDE, FORM BOTH CHROMOSOME ABERRATIONS AND
MICRONUCLEI?

A  IT DOES.

Q  AND DO THE OTHER CLASTOGENS IN COFFEE THAT
YOU'VE IDENTIFIED ALSO DO THAT?

A  THEY DO.

Q  NOW, DO YOU READ STUDIES REGARDING THE
MECHANISM OF CHILDHOOD LEUKEMIA AS THEY ARE PUBLISHED?

A  YES.

Q  THAT'S A FIELD OF RESEARCH THAT YOU KEEP UP ON?

A  YES.
Q AND HOW DO YOU KEEP UP ON THAT?
A THERE'S ALL SORTS OF MECHANISMS THESE DAYS: THROUGH RESEARCHGATE, LINKEDIN, AND VARIOUS WEBSITES LIKE THAT. PLUS, WE REGULARLY SEARCH THE PUBMED LITERATURE AND HAVE ALERTS SENT TO US ABOUT PARTICULAR TOPICS.
Q OKAY. ARE YOU AWARE OF ANY STUDY THAT CLAIMS TO HAVE DISPROVED THE MECHANISM OF CHILDHOOD LEUKEMIA FROM CLASTOGENS CAUSING CHROMOSOME DAMAGE?
A NO.
Q NOW, IS THIS MECHANISM THAT YOU HAVE DESCRIBED AS BEING GENERALLY -- WELL, THAT MECHANISM, I UNDERSTAND -- IS IT YOUR TESTIMONY THAT MECHANISM IS GENERALLY ACCEPTED?
A YES.
MR. SCHURZ: OBJECT, AND -- INTERPOSE AN OBJECTION AS TO WHAT IS -- VAGUE AND AMBIGUOUS AS TO "MECHANISM"; AND AGAIN, LACKS FOUNDATION AS TO THIS WITNESS'S --
THE COURT: SUSTAINED.
Q BY MR. METZGER: WOULD YOU CLEARLY DEFINE FOR US THE MECHANISM OF CHILDHOOD LEUKEMOGENESIS THAT YOU CONSIDER TO BE GENERALLY ACCEPTED IN THE SCIENTIFIC COMMUNITY.
A THE GENERALLY ACCEPTED MECHANISM IS THAT WITHIN THE FETUS, CHROMOSOME Damage OCCURS WITHIN THE STEM CELLS OF EITHER THE LIVER OR THE BONE MARROW; AND THAT THESE GENETIC CHANGES, THESE CHROMOSOMAL CHANGES, ARE RETAINED AT BIRTH;
AND THAT CERTAIN -- THE SECOND -- AS THE CHILD IS BORN AND THE IMMUNE SYSTEM DEVELOPS, THE THINKING THEN IS THAT THESE CELLS CAN EITHER DIE OUT, AND THE CHILD DOES NOT GET LEUKEMIA;

OR THAT OTHER FACTORS -- PROBABLY RELATED TO LIFE STYLES SUCH AS BREAST FEEDING, BIRTH ORDER, AND THINGS LIKE THIS, TO DO WITH THE DEVELOPMENT OF THE IMMUNE SYSTEM -- LEAD TO THE CLONING OUT OF THOSE CELLS IN SOME CHILDREN TO PRODUCE LEUKEMIA.

THIS IS THE GENERALLY ACCEPTED IDEA OF HOW CHILDHOOD LEUKEMIA DEVELOPS. IT'S BEEN WRITTEN ABOUT BY MEL GREAVES, WHO IS THE WORLD'S LEADING EXPERT ON CHILDHOOD LEUKEMIA AND WHO HAS EXTENSIVELY WRITTEN ON THIS TOPIC; AND IS GENERALLY ACCEPTED BY MEMBERS OF THE SCIENTIFIC COMMUNITY AS BEING WHAT WE KNOW TO DATE ABOUT CHILDHOOD LEUKEMIA.

Q AND WOULD YOU DEFINE FOR US WHAT YOU MEAN BY "CHROMOSOME ABERRATIONS," SPECIFICALLY, IN THIS MECHANISM.

A I MEAN STRUCTURAL CHANGES TO THE CHROMOSOMES, WHERE PART OF ONE CHROMOSOME IS MOVED TO ANOTHER CHROMOSOME, OR PART OF A CHROMOSOME IS TWISTED AROUND, OR PART OF A CHROMOSOME IS LOST OR GAINED, AND THERE IS NOT A NORMAL COMPLEMENT OF CHROMOSOMES WITHIN THE CELLS.

Q AND ARE THOSE CHANGES THAT YOU'VE JUST DESCRIBED THE CHANGES THAT ARE CAUSED BY CHEMICAL CLASTOGENS?
A THAT COULD BE ONE CAUSE. IT'S ALSO POSSIBLE
THAT THEY COULD ARISE JUST BY RANDOM ERRORS IN THE CELL.
BUT IT'S MUCH MORE LIKELY THAT THEY'RE CAUSED BY
CHEMICAL AGENTS OR RADIATION, WHICH WOULD PRODUCE VERY
SIMILAR CHANGES IN THE CHILDREN'S CELLS.

Q OKAY. NOW, IS THE MECHANISM FOR CHILDHOOD
LEUKEMIA THAT YOU HAVE DESCRIBED THE SAME THING AS A
HYPOTHESIS THAT CONSUMPTION OF FRUITS AND VEGETABLES
DURING PREGNANCY CAUSES CHILDHOOD LEUKEMIA?

A NO, NOT AT ALL.

Q WOULD YOU EXPLAIN.

A WELL, THE IDEA THAT THESE CHROMOSOME CHANGES
OCUR IN UTERO AND THEY DEVELOP INTO A LEUKEMIA IN THE
GROWING CHILD IS ALL RELATED TO STUDIES IN TWINS, WHERE
WE KNOW THAT IDENTICAL TWINS WILL BE AT HIGHER RISK OF
LEUKEMIA; THAT MONOZYGOTIC TWINS ARE AT INCREASED RISK.

WE KNOW THAT THE CHROMOSOME CHANGES ARE
PRESENT AT BIRTH. WE KNOW -- WE CAN ACTUALLY IDENTIFY
THEM IN THE SPECIFIC PATIENTS.

ALL OF THIS TYPE OF INFORMATION IS USED TO
BUILD THE HYPOTHESIS OR THE KNOWLEDGE THAT WE HAVE NOW
ABOUT HOW CHILDHOOD LEUKEMIA ARISES. IT'S GOT NOTHING
TO DO WITH FRUITS AND VEGETABLES.

Q ALL RIGHT. WOULD YOU TELL THE COURT WHAT A
TRANSPLACENTAL CARCINOGEN IS.

A A CHEMICAL THAT'S CONSIDERED TO BE A
TRANSPLACENTAL CARCINOGEN IS A CHEMICAL THAT WILL CROSS
FROM THE MOTHER INTO THE FETUS AND CAUSE DAMAGE, WHICH
THEN, ONCE THE FETUS IS BORN AND BECOMES A VIABLE PERSON -- AS THEY GROW, THEY CAN DEVELOP CANCER. AND SO IT'S THE PRODUCTION OF CANCER IN THE OFFSPRING OF SOMEONE.

Q IN TRANSPLACENTAL CARCINOGENSE, DOES CANCER ACTUALLY MANIFEST IN THE FETUS?

A NO. TYPICALLY, LATER IN LIFE.

THE MOST CLASSIC EXAMPLE IS ACTUALLY THE MOTHERS WHO TOOK THE DRUG DIETHYLSTILBESTROL. THE DRUG CROSSED INTO THE PLACENTA, DAMAGED THE FETUS, AND THE CHILDREN THEN DEVELOPED CANCERS MUCH LATER IN LIFE, WHEN THEY WERE TEENAGERS OR BEYOND. THAT'S THE CLASSICAL TRANSPLACENTAL CARCINOGEN.

Q OKAY. IS THERE A RELATIONSHIP BETWEEN TRANSPLACENTAL CARCINOGENS AND REPRODUCTIVE TOXINS?

A YES. ALMOST ANYTHING THAT WILL CROSS THE PLACENTA AND DAMAGE THE DNA -- SUCH AS ACRYLAMIDE, SUCH AS DIETHYLSTILBESTROL -- WILL HAVE THE POTENTIAL OF CAUSING NOT ONLY CANCER IN OFFSPRING FROM THAT DAMAGE, BUT THAT GENETIC DAMAGE COULD ALSO LEAD TO BIRTH DEFECTS AND OTHER DEVELOPMENTAL DEFECTS IN THE OFFSPRING. SO THEY'RE KIND OF ONE AND THE SAME THING.

Q OKAY. HAS THE U.S. EPA DETERMINED HOW RISKS OF TRANSPLACENTAL CARCINOGENSES SHOULD BE ASSESSED?

A YES. SO THEY -- IN THEIR GUIDELINES FOR RISK ASSESSMENT FOR DEVELOPMENTAL TOXICANTS, THEY REALIZED THAT SOME DEVELOPMENTAL TOXICANTS -- SOME CHEMICALS WHICH WOULD CAUSE BIRTH DEFECTS AND THESE
TYPES OF EVENTS, THESE ADVERSE EVENTS, COULD ALSO
POTENTIALLY CAUSE CANCER IN THE OFFSPRING.
Q I'D LIKE TO SHOW YOU WHAT'S BEEN MARKED AS
EXHIBIT 351, A DOCUMENT ENTITLED "GUIDELINES FOR
DEVELOPMENTAL TOXICITY RISK ASSESSMENT OF THE U.S. EPA."
IS THIS WHAT YOU ARE REFERRING TO?
A YES.
(EXHIBIT 351 MARKED FOR IDENTIFICATION.)
Q BY MR. METZGER: ALL RIGHT. AND IS THERE A
PARTICULAR STATEMENT IN THIS GUIDELINE PREPARED BY THE
EPA REGARDING HOW TRANSPLACENTAL -- THE RISK OF
TRANSPLACENTAL CARCINOGENESIS SHOULD BE ASSESSED?
A YES. IT SAYS THAT --
Q WHERE ARE YOU, PLEASE?
A I'M SORRY. ON PAGE 5, THERE'S AN INFORMED
STATEMENT.
Q AND WOULD YOU READ THAT, PLEASE.
A SO IT'S --
MR. SCHURZ: I'LL OBJECT AS HEARSAY. WE'RE NOT
HERE TO HAVE THE WITNESS READ INTO THE RECORD --
THE COURT: OBJECTION SUSTAINED.
MR. METZGER: ALL RIGHT. YOUR HONOR, I WOULD
REQUEST JUDICIAL NOTICE OF EXHIBIT 351. IT'S AN EPA
CANCER -- IT'S AN EPA GUIDELINE THAT'S RELEVANT TO THIS
MATTER.
THE COURT: ANY OBJECTION?
MR. SCHURZ: YES, YOUR HONOR. WE WOULD OBSERVE,
THIS IS THE SUBJECT OF A WRITTEN MOTION, OR A REQUEST
FOR JUDICIAL NOTICE. WE INTEND TO OPPOSE THAT. IT'S NOT CLEAR WHY THIS IS BEING PROVIDED TO US ON OCTOBER THE 14TH, WHEN THESE THINGS WERE ALL DUE ON AUGUST THE 1ST.

BUT QUITE APART FROM ITS TIMELINESS, WE WILL BE FILING WITH THE COURT A RESPONSE TO THE REQUEST FOR JUDICIAL NOTICE AND WOULD ASK THAT THE COURT CONSIDER THAT.

THE COURT: ALL RIGHT. WE'LL HOLD OFF ON THAT, REGARDING THE JUDICIAL NOTICE.

NEXT.

Q     BY MR. METZGER: ALL RIGHT. PROFESSOR SMITH, DO YOU CONSIDER IT APPROPRIATE TO USE THE U.S. EPA GUIDELINES FOR CARCINOGEN RISK ASSESSMENT TO ASSESS THE RISKS OF TRANSPLACENTAL CARCINOGENICITY?

A     I DO.

Q     AND WHAT IS YOUR BASIS FOR THAT OPINION?

A     THE BASIS OF THAT IS THE OPINION OF THE U.S. EPA IN THEIR CANCER RISK ASSESSMENT GUIDELINES, IN THESE GUIDELINES FOR DEVELOPMENTAL TOXICANTS: THAT ANY DEVELOPMENTAL TOXICANT WHICH ALSO HAS CARCINOGENIC EFFECTS, EITHER ON THE FETUS OR ON THE OFFSPRING, THROUGH EXPOSURE OF THE MOTHER, SHOULD BE EVALUATED AS A -- UNDER THE CARCINOGENIC GUIDELINES, NOT UNDER THE DEVELOPMENTAL TOXICITY GUIDELINES.

MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT AND MOVE TO STRIKE AS AN UNDISCLOSED OPINION, AS EVIDENCED BY THE FACT THAT WE'RE SEEING THIS DOCUMENT IN OCTOBER. THIS
IS NOT PART OF DR. SMITH'S ORIGINAL SET OF OPINIONS, IT
WAS NOT THE SUBJECT OF HIS DEPOSITION TESTIMONY, AND
THIS IS THE FIRST TIME WE'RE HEARING IT.

THE COURT: ALL RIGHT. MR. METZGER?

MR. METZGER: WE WERE TOTALLY SURPRISED BY THE
DEFENSE CONTENTION THAT TRANSPLACENTAL CARCINOGENESIS IS
REPRODUCTIVE TOXICITY AND NOT CARCINOGENESIS. SO WE --

THE COURT: ALL RIGHT. WE'LL ARGUE THAT LATER.

YOU CAN RENEW YOUR MOTION TO STRIKE LATER. AT THIS
TIME, THE COURT WILL ALLOW IT.

NEXT QUESTION.

Q BY MR. METZGER: ALL RIGHT. PROFESSOR

SMITH, WOULD YOU TELL THE COURT YOUR CONCLUSIONS AS TO
WHETHER ACRYLAMIDE PRESENTS A RISK OF CANCER TO INFANTS
AND CHILDREN FROM TRANSPLACENTAL EXPOSURE.

A YES. SO ACRYLAMIDE IS CAPABLE OF CROSSING
INTO THE FETUS FROM THE MOTHER. IT'S ALSO CAPABLE OF
BEING CONVERTED BY THE MOTHER INTO GLYCIDAMIDE, WHICH
WILL CROSS INTO THE FETUS, WHERE THEY WILL POTENTIALLY
DAMAGE THE DNA IN MANY WAYS THAT WE'VE DISCUSSED TODAY
AND THEREFORE PRESENT A RISK OF TRANSPLACENTAL
CARCINOGENESIS.

Q OKAY. AND WOULD YOU TELL THE COURT YOUR
CONCLUSION AS TO WHETHER ACRYLAMIDE SHOULD BE TREATED
AND REGULATED AS A PROBABLE HUMAN CARCINOGEN.

MR. SCHURZ: OBJECTION; LEADING.

THE COURT: OVERRULED.

THE WITNESS: YES. SO THERE ARE MULTIPLE ANIMAL
STUDIES THAT I’VE ALREADY MENTIONED THAT HAVE LED THE IARC AND NTP AND THE EPA AND ALL AUTHORITATIVE BODIES TO CONCLUDE THAT ACRYLAMIDE IS A PROBABLE HUMAN CARCINOGEN.

THE FACT THAT IT’S ALSO GENOTOXIC, AND IS METABOLIZED TO A HIGHLY GENOTOXIC METABOLITE WHICH ALSO PRODUCES CANCER IN MANY SITES IN ANIMALS, MEANS THAT WE SHOULD DEFINITELY CONSIDER IT AS A GENOTOXIC PROBABLE HUMAN CARCINOGEN.

Q AND LASTLY, WOULD YOU TELL THE COURT YOUR CONCLUSION AS TO WHETHER ACRYLAMIDE IN COFFEE POSES A RISK OF HUMAN CANCER, INCLUDING CHILDHOOD LEUKEMIA.

A WELL, BECAUSE OF ITS PRESENCE IN COFFEE AND THE FACT THAT MATERNAL EXPOSURE TO COFFEE COULD THEN LEAD TO FETAL EXPOSURE TO ACRYLAMIDE AND GLYCIDAMIDE, IT WILL THEREFORE PRESENT A RISK OF FUTURE CANCER IN THE FETUS.

MR. METZGER: THANK YOU VERY MUCH, PROFESSOR SMITH.

I HAVE NO FURTHER QUESTIONS AT THIS TIME.

THE COURT: ALL RIGHT. THANK YOU.

MR. SCHURZ.

CROSS-EXAMINATION

BY MR. SCHURZ:

Q GOOD MORNING, DR. SMITH.

A GOOD MORNING.

Q NOW, EARLIER, IN YOUR DISCUSSION WITH MR. METZGER, YOU TESTIFIED THAT ACRYLAMIDE IS DISTRIBUTED TO
THE FETUS; IS THAT CORRECT?
   A  CORRECT.
   Q  AND NONE OF THE STUDIES THAT YOU HAVE LOOKED
   AT AND PROVIDED AS PART OF YOUR RELIANCE MATERIALS HAVE
   DETECTED ACTUAL DNA ADDUCTS FOR ACRYLAMIDE OR
   GLYCIDAMIDE IN THE HUMAN PLACENTA; CORRECT?
   A  I DON'T THINK THAT'S BEEN EXAMINED, NO.
   Q  AND IN FACT, IN THE ANOLA (PHONETIC) STUDY,
   WHICH YOU DID REVIEW, THE AUTHORS REPORTED LOOKING FOR
   BUT NOT FINDING ACRYLAMIDE- AND GLYCIDAMIDE-DNA ADDUCTS
   IN PLACENTAL TISSUE; CORRECT?
   A  I DON'T RECALL. I'D HAVE TO LOOK AT THAT
   STUDY.
   Q  ALL RIGHT. YOU EARLIER TESTIFIED WITH
   RESPECT TO FLAVONOIDS ACTING AS CLASTOGENS. DO YOU
   RECALL THAT TESTIMONY?
   A  YES.
   Q  AND YOU'VE WRITTEN ON THE ISSUE OF
   FLAVONOIDS, HAVE YOU NOT?
   A  I HAVE.
   Q  AND IN A 2000 ARTICLE THAT YOU PREPARED WITH
   CHRISTINE SKIBOLA, YOU CONCLUDED THAT THE LEVEL OF
   FLAVONOIDS REQUIRED TO INDUCE MUTATIONS AND CYTOTOXICITY
   MAY NOT BE PHYSIOLOGICALLY ACHIEVABLE THROUGH DIETARY
   SOURCES, DID YOU NOT?
   A  I DID.
   Q  AND WHAT YOU WERE LOOKING AT WITH FLAVONOIDS
   IS THE POTENTIAL IMPACT OF WHAT YOU REFERRED TO AS
EXCESSIVE FLAVONOID INTAKE; CORRECT?

A YES.

Q AND WHAT YOU WERE SPECIFICALLY LOOKING AT WERE ISSUES WITH RESPECT TO SUPPLEMENTS; CORRECT?

A THAT'S CORRECT.

Q AND SO WITH RESPECT TO NORMAL DIETARY LEVELS OF FLAVENOIDS, YOUR CONCLUSION WAS THAT THOSE LEVELS, IN THE DIETARY LEVELS, MAY NOT BE SUFFICIENT TO INDUCE MUTATIONS; CORRECT?

A I THINK WHAT WE SAID WAS THAT THEY MAY NOT BE SUFFICIENT TO POSE A RISK OF MUTATION IN ADULTS, BUT WE WERE CONCERNED IN THAT ARTICLE ABOUT THE POTENTIAL RISK OF CHILDHOOD LEUKEMIA FROM MATERNAL EXPOSURE TO FLAVONOIDS, HIGH INTAKE OF FLAVONOIDS.

Q AND BASED UPON THAT INTEREST, YOU DETERMINED THAT THE LEVEL OF FLAVONOIDS REQUIRED TO INDUCE MUTATIONS AND CYTOTOXICITY MAY NOT BE PHYSIOLOGICALLY ACHIEVABLE THROUGH DIETARY SOURCES; CORRECT?

A CORRECT.

Q LET ME TURN TO THE TOPOISOMERASE II INHIBITOR THEORY THAT YOU DISCUSSED WITH MR. METZGER. THE DNA TOPOISOMERASE II IS AN ENZYME THAT'S INVOLVED IN THE UNWINDING AND RE-LIGATION OF DNA; CORRECT?

A CORRECT.

Q AND INHIBITORS -- TOPOISOMERASE II INHIBITORS ARE COMPOUNDS THAT INTERFERE WITH THAT FUNCTION; IS THAT CORRECT?

A THAT'S CORRECT.
Q AND SHOWING YOU NOW THE ROSS 1996 STUDY, WHICH HAS BEEN IDENTIFIED AS EXHIBIT 1847; AND YOU'LL SEE IT THERE ON YOUR SCREEN. IS THIS THE ARTICLE THAT YOU REVIEWED AS PART OF YOUR WORK IN THIS CASE?

A YES.

(EXHIBIT 1847 MARKED FOR IDENTIFICATION.)

Q BY MR. SCHURZ: AND DID YOU RELY ON THIS STUDY IN PREPARING YOUR OPINIONS IN THIS CASE?

A YES.

Q NOW -- AND WE'VE GOT A HARD COPY COMING TO YOU.

NOW, PROFESSOR ROSS, IN HER 1996 PAPER, IDENTIFIES A BROAD RANGE OF NATURALLY OCCURRING TOPOISOMERASE II INHIBITORS, DOES SHE NOT?

A SHE DOES.

Q AND THOSE COMPOUNDS ARE FOUND IN -- COMMONLY FOUND IN FRUITS AND VEGETABLES; CORRECT?

A CORRECT.

Q AND THEY'RE -- THESE TOPOISOMERASE II INHIBITORS ARE COMMONLY FOUND IN SOY BEANS; CORRECT?

A YES.

Q AND THEY'RE ALSO FOUND IN GREEN AND BLACK TEA, COCOA, WINE, AS WELL AS COFFEE; IS THAT CORRECT?

A CORRECT.

Q ALL RIGHT. NOW, THE HYPOTHESIS THAT WAS TESTED BY DR. ROSS IS THAT CONSUMPTION OF THESE FOODS THAT CONTAIN TOPOISOMERASE II INHIBITORS MAY BE
ASSOCIATED WITH AN INCREASED RISK OF CHILDHOOD LEUKEMIA
IN THE OFFSPRING; CORRECT?

A CORRECT.

Q AND SHE REPORTED HER RESULTS WITH RESPECT TO
THE VARIOUS FOODS THAT SHE IDENTIFIED -- A PRIORITY AS
TO HAVING TOPOISOMERASE II INHIBITORS; CORRECT?

A SHE DID, YES.

Q SO LET ME TURN YOUR ATTENTION TO TABLE 1, AT
PAGE 004 OF EXHIBIT 1847. AND DO YOU HAVE THAT IN FRONT
OF YOU?

A I DO.

Q SO AMONG THE THINGS THAT DR. ROSS NOTED OR
REPORTED WAS A 13-FOLD -- EXCUSE ME, AN INCREASED RISK
OF 13.7 ASSOCIATED WITH FRESH VEGETABLES. DO YOU SEE
THAT?

A YES.

Q AND SHE ALSO INDICATED AN 8.8 INCREASED RISK
FOR CONSUMPTION OF BEANS. DO YOU SEE THAT?

A YES.

Q TO YOUR KNOWLEDGE, HAS ANY GOVERNMENT
REGULATORY AGENCY ADVISED PREGNANT WOMEN TO DECREASE
THEIR CONSUMPTION OF FRESH VEGETABLES DURING PREGNANCY
BECAUSE IT MAY RESULT IN AN INCREASED INCIDENCE OF
CHILDHOOD LEUKEMIA?

A NO.

Q AND HAS ANY GOVERNMENT AGENCY ADVISED
PREGNANT WOMEN NOT TO EAT BEANS DURING PREGNANCY BECAUSE
IT MAY LEAD TO AN INCREASED RISK OF CHILDHOOD LEUKEMIA
IN THEIR OFFSPRING?

A NO.

Q LET'S TURN NOW TO --

THANK YOU. NOTHING FURTHER WITH RESPECT TO THIS EXHIBIT.

YOU INDICATED THAT THE TOPOISOMERASE II INHIBITION THEORY OF DR. ROSS HAS BEEN THE SUBJECT OF SUBSEQUENT INVESTIGATION; IS THAT CORRECT?

A CORRECT.

Q AND YOU CITED THE SPECTOR INVESTIGATION; CORRECT?

A CORRECT.

Q THERE ARE AT LEAST THREE SEPARATE PEER-REVIEWED ARTICLES TESTING THE HYPOTHESIS, ARE THERE NOT?

A THERE'S THE SPECTOR ARTICLE. I'M NOT AWARE OF THE OTHERS.

Q ALL RIGHT. THAT WAS MY NEXT QUESTION.

HAVE YOU REVIEWED ANY OF THE OTHER ARTICLES EVALUATING AND TESTING THE TOPOISOMERASE II INHIBITOR THEORY, OTHER THAN SPECTOR?

A NO.

Q LET'S TAKE A LOOK AT THE SPECTOR ARTICLE, WHICH IS EXHIBIT 1980.

AND WE'VE GOT A HARD COPY ON ITS WAY TO YOU; BUT BASED ON THE ARTICLE THAT APPEARS ON THE SCREEN, CAN YOU IDENTIFY FOR US EXHIBIT 1980.

A IT'S THE ARTICLE BY LOGAN SPECTOR AND
OTHERS, PUBLISHED IN 2005.

(EXHIBIT 1980 MARKED FOR IDENTIFICATION.)

Q  BY MR. SCHURZ:  DID YOU REVIEW THIS ARTICLE AS PART OF WORK IN THIS CASE?

A  I DID.

Q  DID YOU RELY ON THIS ARTICLE IN FORMING YOUR OPINIONS?

A  I DID.

Q  NOW, THIS WAS THE LARGEST STUDY EVALUATING DIETARY EXPOSURES TO TOPO ISOMERASE II INHIBITOR FOODS; CORRECT?

A  CORRECT.

Q  AND THIS GROUP OF AUTHORS ALSO INCLUDES DR. ROSS, DOES IT NOT?

A  IT DOES.

Q  NOW, LET'S TAKE A LOOK -- IF I CAN DIRECT YOUR ATTENTION TO TABLE NO. 3, AT PAGE 0004 OF EXHIBIT 1980.  AND DO YOU HAVE THAT IN FRONT OF YOU?

A  I DO.

Q  AND HERE, THE AUTHORS WERE AGAIN TESTING THE HYPOTHESIS THAT THEY HAD LOOKED AT IN THEIR EARLIER EXPLORATORY STUDY AND WERE EVALUATING WHETHER THOSE TOPOISOMERASE-CONTAINING FOODS THAT THEY HAD ANALYZED IN THE FIRST INVESTIGATION SHOWED AN INCREASED RISK OF ACUTE LEUKEMIA; CORRECT?

A  CORRECT.

Q  AND IN THIS CONTEXT, UNLIKE THE PRIOR STUDY,
WHAT THEY FOUND WAS, IN LOOKING AT THE TOPOISOMERASE II FOODS -- THAT THEY'VE IDENTIFIED AS THE VF-PLUS INDEX.
DO YOU SEE THAT?
A  YES.
Q AND THE "VF-PLUS INDEX" REFERS TO VEGETABLES AND FRUIT PLUS OTHER TOPOISOMERASE II-CONTAINING --
INHIBITOR-CONTAINING FOODS; CORRECT?
A  CORRECT.
Q  ALL RIGHT. AND WITH RESPECT TO THESE VALUES, WHAT THE AUTHORS FOUND WAS THE ABSENCE OF ANY INCREASED ASSOCIATION OR INCREASED RISK OF ACUTE LEUKEMIA AND INCREASING CONSUMPTION OF THE FRUITS-AND-VEGETABLES-PLUS INDEX; CORRECT?
A  YES.
Q  IN FACT, WHAT THEY FOUND IN CERTAIN CASES WAS A STATISTICALLY SIGNIFICANT DECREASED RISK, DID THEY NOT?
A  WELL, IT'S MARGINAL WITH REGARDS TO -- YES. AT THE TOP, IT'S STATISTICALLY SIGNIFICANT TO MLL PLUS, YES.
Q  ALL RIGHT. AND THE AUTHORS DID NOT FIND ANY STATISTICALLY SIGNIFICANT INCREASE ASSOCIATED WITH EITHER OF THE DNA-TOPOISOMERASE II-INHIBITOR FOOD INDICES THEY CREATED; CORRECT?
A  WHAT THEY DID FIND WAS A CONFIRMATION OF THEIR EARLIER STUDY, WHICH WAS THAT THE MLL PLUS AML, THERE WAS A SIGNIFICANTLY INCREASED RISK.
Q  WAS IT STATISTICALLY SIGNIFICANT?
A WELL, IT'S 3.2-FOLD. I AGREE, IT'S NOT STATISTICALLY SIGNIFICANT, AND THE TREND IS MARGINAL; BUT IT'S A VERY, VERY SMALL NUMBER OF CASES.

Q THANK YOU, DR. SMITH.

LET'S TALK A LITTLE BIT NOW ABOUT ACRYLAMIDE IN THE CONTEXT OF THE -- AS A TOPOISOMERASE II POTENTIAL INHIBITOR. YOU TESTIFIED, DR. SMITH, THAT COFFEE INHIBITS TOPOISOMERASE II; IS THAT CORRECT?

A I TESTIFIED THAT SOME OF THE COMPOUNDS IN COFFEE, INCLUDING ACRYLAMIDE, WOULD INHIBIT TOPOISOMERASE II.

Q AND THAT IT IS YOUR OPINION THAT THIS INHIBITION OF TOPOISOMERASE II COULD LEAD TO CHROMOSOME BREAKS THAT CONTRIBUTE TO CHILDHOOD LEUKEMIA; CORRECT?

A AS I MENTIONED EARLIER, IT COULD BE ONE OF THREE PLAUSIBLE MECHANISMS, YES.

Q RIGHT. NOW, AS PART OF YOUR WORK IN THIS CASE, YOU DID NOT REVIEW THE STUDIES INVESTIGATING THE MUTAGENICITY OF BREWED COFFEE; CORRECT?

A I DID NOT.

Q NOW, SHOWING YOU WHAT HAS BEEN MARKED FOR IDENTIFICATION PURPOSES AS EXHIBIT 1907. THIS IS A PAPER BY GIULIA SCIANDRELLO. AND CAN YOU IDENTIFY THAT PAPER FOR US, DR. SMITH.

A YES. THIS IS A PAPER THAT I CITED IN MY REPORT.

(Exhibit 1907 marked for identification.)
Q BY MR. SCHURZ: SO THAT WAS MY NEXT QUESTION. IS THIS -- DID YOU RELY ON THIS PAPER IN FORMING YOUR OPINIONS?
A YES.
Q ALL RIGHT. AND THIS PAPER IS TITLED "ACRYLAMIDE CATALYTICALLY INHIBITS TOPOISOMERASE II IN V79 CELLS"; CORRECT?
A CORRECT.
Q NOW, THERE ARE GENERALLY RECOGNIZED TO BE TWO CATEGORIES OF TOPOISOMERASE II INHIBITORS, ARE THERE NOT?
A YES.
Q AND ONE SUCH CATEGORY IS A TOPOISOMERASE II POISON; CORRECT?
A CORRECT.
Q AND THE SECOND CATEGORY WOULD BE A TOPOISOMERASE II CATALYTIC INHIBITOR; CORRECT?
A CORRECT.
Q AND AS OUTLINED HERE IN THE SCIANDRELLO PAPER, ACRYLAMIDE IS A -- IS OF THAT SECOND CATEGORY: IT IS A CATALYTIC INHIBITOR; CORRECT?
A CORRECT.
Q AND THAT, MOREOVER, ACRYLAMIDE DOES NOT ACT AS A TOPOISOMERASE II POISON; CORRECT?
A CORRECT.
Q ALL RIGHT. NOW, LET'S DISCUSS FOR A MOMENT THE SIGNIFICANCE OF THAT CATEGORY. AND LET ME SHOW YOU NOW ANOTHER ARTICLE THAT WAS PART OF YOUR PRODUCTION.
I'm showing you Exhibit 1468, an article by Miguel Lopez-Lazaro from 2011. And can you identify this document for us.

As you just mentioned.

(EXHIBIT 1468 MARKED FOR IDENTIFICATION.)

Q by Mr. Schurz: And did you rely on this document -- well, strike that. Did you review this document?

A I believe so, yes.

Q And did you rely on this document in forming your opinions in this case?

A Not strongly, no.

Q All right. We did observe that it was cited in your materials. Is it the case that you did not rely on this document in forming your opinions in this case?

A It's not necessary to my opinions.

Q All right. Well, let's talk for a moment, then, with respect to the consequence of the categories that we've been discussing: Topo 2 poisons and Topo 2 catalytic inhibitors.

Let's start with catalytic inhibitors. Now, is it the case that catalytic inhibitors are generally associated with cell death; is that correct?

A There is some debate about that, and there is also debate about the misclassification of catalytic versus poison.

Neil Osheroff now believes that all of these
ARE ALL POISONS WORKING ON DIFFERENT SITES WITHIN THE
TOPOISOMERASE II AND THAT THE SEPARATION OF THE
CATALYTIC AND POISONS IS SOMEWHAT ARTIFICIAL;

THAT THEY REALLY SHOULD BE TALKING ABOUT THE
TARGETING OF PARTICULAR DOMAINS IN THE ENZYME, EITHER OF
THE ATPA'S OR OF THE CATALYTIC COMPONENT, WHICH I
MENTIONED -- WHICH I SHOWED AS THE HEART-SHAPED
COMPONENT OF THE PROTEIN.

SO THIS SEPARATION OF CATALYTIC VERSUS -- IS
SOMewhat ARBITRARY. AND I AGREE WITH YOU THAT CATALYTIC
INHIBITORS TEND TO LEAD TO CELL DEATH BECAUSE THEY ARE
SO EFFICIENT AT PRODUCING DOUBLE-STRAND BREAKS.

Q AND BY CONTRAST, THE TOPO 2 POISONS ARE
GENERALLY ASSOCIATED WITH BREAKS IN DNA STRANDS;
CORRECT?

A WELL, BOTH OF THEM PRODUCE BREAKS IN DNA
STRANDS, BUT THE CATALYTIC ONES PRODUCE SEVERE DOUBLE-
STRAND BREAKS. AND SO THIS IS RECOGNIZED BY THE CELL AS
SOMETHING WHICH IS POTENTIALLY VERY CARCINOGENIC; AND SO
OFTEN LEADS TO THIS FALLACY, AS WELL.

Q WELL, BUT AGAIN, RELYING ON THOSE DOCUMENTS
THAT WERE PRODUCED AS PART OF YOUR RELIANCE MATERIALS,
DON'T THE LOPEZ-LAZARO INVESTIGATORS CONCLUDE THAT
TOPOISOMERASE II CATALYTIC INHIBITORS ACTUALLY PROTECT
AGAINST STRAND BREAKS BY PREVENTING TOPOISOMERASE II
FROM BINDING WITH DNA?

A NO, I DON'T BELIEVE SO. WHAT THEY WILL DO
IS PREVENT THE POISONS FROM BINDING TO THE PROTEIN AND
THEREFORE ACTING. SO THEY PREVENT THE THINGS LIKE THE
PODOXYLLOTOXINS FROM ACTING ON THE TOPO II. BUT THEY
ALL -- ALL THE CATALYTIC INHIBITORS WILL ALSO PRODUCE
STRAND BREAKS AND BREAK THE DNA.

Q ALL RIGHT. BUT THESE CATALYTIC INHIBITORS, AS REPORTED BY LOPEZ-LAZARO, WILL ACTUALLY ACT TO
ANTAGONIZE CERTAIN TOPOISOMERASE II POISONS; IS THAT CORRECT?
A THEY'LL ANTAGONIZE THEM, YES.
Q OKAY. NOW, WE LOOKED AT, EARLIER, SLIDE NO. 35, THAT WAS INCLUDED IN YOUR PRODUCTION. AND IF WE COULD TAKE A LOOK AT THAT NOW. IT WAS ENTITLED "CONCURRENCE WITH THE WHO."
AND YOU INDICATED THAT YOU HAVE -- THAT YOU CONCUR WITH THE RECOMMENDATION OF THE WORLD HEALTH ORGANIZATION, AS ARTICULATED HERE; CORRECT?
A I CONCUR WITH THEIR -- THAT'S NOT REALLY A RECOMMENDATION. IT'S REALLY A COMMENT OR AN OPINION.
Q AND THE WHO HAS NOT RECOMMENDED THAT PEOPLE REFRAIN FROM DRINKING COFFEE AS A RESULT OF THE CONTENT OF ACRYLAMIDE; CORRECT?
A NO, THEY HAVE NOT.
Q AND THE WHO HAS RECOMMENDED FURTHER EFFORTS AT DEVELOPING AND IMPLEMENTING MITIGATION MEASURES FOR ACRYLAMIDE IN FOODS OF MAJOR IMPORTANCE FOR DIETARY EXPOSURE, HAVE THEY NOT?
A YES.
Q AND THE WHO HAS NOT IDENTIFIED COFFEE FOR
ANY MITIGATION MEASURE; CORRECT?

MR. METZGER: OBJECTION. YOUR HONOR, THIS IS THE NEXT PHASE. WE'RE NOW IN MITIGATION. I'VE BEEN PRECLUDED FROM OFFERING ANY EVIDENCE ABOUT MITIGATION IN THIS TRIAL, SO I OBJECT.

THE COURT: OVERRULED.

THE WITNESS: I'M NOT AWARE OF WHAT THE WHO'S SPECIFIC OPINIONS ARE ON MITIGATION AT THIS TIME.

Q BY MR. SCHURZ: ALL RIGHT. NOW, HAVE YOU SPOKEN ABOUT YOUR OPINIONS WITH ANY OF THE OTHER EXPERT WITNESSES RETAINED BY CERT?

A NO.

Q DID YOU DISCUSS WITH DR. RAPPAPORT HIS OPINIONS THAT HE WAS OFFERING WITH RESPECT TO THIS MATTER?

A I DISCUSSED ONLY GENERALLY HIS THINKING ABOUT THE POINTS OF DEPARTURE AND OTHER ASPECTS OF DOSE-RESPONSE ANALYSIS UNDER EPA GUIDELINES.

Q AND DO YOU KNOW IF YOUR OPINIONS WITH RESPECT TO THOSE ISSUES UPON WHICH YOU AND DR. RAPPAPORT OVERLAPPED -- WHETHER THERE ARE ANY DIFFERENCES IN THE OPINIONS THAT THE TWO OF YOU ARE OFFERING?

A I DON'T KNOW OF ANY DIFFERENCES.

Q NOW, WITH RESPECT TO DR. MELNICK, ARE YOU AWARE OF WHAT DR. MELNICK HAS TESTIFIED TO WITH RESPECT TO THOSE ISSUES ON WHICH YOU TWO OVERLAP?

MR. METZGER: WELL, OBJECTION; LACKING IN FOUNDATION.
THE COURT: OVERRULED.

THE WITNESS: I HAVE NOT DISCUSSED ANY OF DR. MELNICK'S OPINIONS WITH HIM.

Q BY MR. SCHURZ: MY QUESTION WAS SLIGHTLY DIFFERENT. ARE YOU AWARE OF THE OPINIONS THAT DR. MELNICK IS OFFERING THAT OVERLAP WITH YOURS?

THE COURT: ALL RIGHT. OBJECTION IS SUSTAINED.

Q BY MR. SCHURZ: AND DO YOU KNOW, DR. SMITH, WHETHER ANY OF THE OPINIONS THAT YOU'VE OFFERED THIS MORNING ARE ANY DIFFERENT THAN THOSE THAT HAVE BEEN OFFERED BY DR. MELNICK WITH RESPECT TO CHILDHOOD LEUKEMIA AND MATERNAL CONSUMPTION OF COFFEE?

A NO, I DO NOT.

Q ALL RIGHT. NOW, DR. SMITH, YOU WERE AMONG THE FOUNDING -- LET ME TURN TO A NEW TOPIC.

YOU WERE AMONG THE FOUNDING MEMBERS OF THE PLAINTIFF IN THIS CASE, THE COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS; CORRECT?

A CORRECT.

Q YOU WERE A MEMBER OF THE BOARD OF DIRECTORS AT THE TIME OF ITS FOUNDING; CORRECT?

A I WAS.

Q IN FACT, YOU SERVED AS AN OFFICER OF THE BOARD OF DIRECTORS, ACTING AS SECRETARY FOR THE BOARD; IS THAT CORRECT?

A I DID.

Q AND CERT'S PRIMARY ACTIVITY DURING THE PERIOD WHEN YOU SERVED ON THE BOARD OF DIRECTORS WAS
ENGAGING IN LITIGATION; CORRECT?

A    CORRECT.

Q    AND OVER THE YEARS, YOUR DIVISION AT THE
UNIVERSITY OF CALIFORNIA HAS RECEIVED $160,000 IN
UNRESTRICTED GIFTS FROM CERT; IS THAT CORRECT?

A    CORRECT. I DON'T KNOW THE EXACT NUMBER, BUT
THAT SOUNDS ABOUT RIGHT.

Q    ALL RIGHT. AND AMONG YOUR ACTIVITIES ON
BEHALF OF CERT WAS TO SERVE -- TO RECRUIT TESTIFYING
EXPERTS FOR LITIGATION THAT CERT WAS BRINGING; IS THAT
CORRECT?

A    CORRECT.

Q    AND YOU HAVE PERFORMED THAT ROLE, HAVE YOU
NOT, IN IDENTIFYING EXPERTS WHO WILL SERVE AS TESTIFYING
EXPERTS FOR CERT IN LITIGATION; CORRECT?

A    IN ONE LITIGATION: THE BURGER KING VS. CERT
LITIGATION.

Q    AND YOU HAVE BEEN RETAINED TO WORK AS AN
EXPERT FOR PARTIES REPRESENTED BY MR. METZGER IN ROUGHLY
10 TO 15 CASES; IS THAT CORRECT?

A    CORRECT.

MR. SCHURZ: I HAVE NOTHING FURTHER, YOUR HONOR.

THE COURT: MAY THE WITNESS BE EXCUSED?

MR. METZGER: I HAVE JUST ONE BRIEF AREA OF
REDIRECT.

THE COURT: HOW LONG IS IT GOING TO TAKE?

MR. METZGER: THREE MINUTES.

THE COURT: OKAY.
DIRECT EXAMINATION

BY MR. METZGER:

Q PROFESSOR SMITH, MR. SCHURZ ASKED YOU CERTAIN QUESTIONS ABOUT FLAVONOIDS AND FRUITS AND VEGETABLES AND TOPOISOMERASE II INHIBITION.

I WOULD JUST LIKE TO ASK YOU THIS: THE OPINION THAT YOU RENDERED REGARDING THE CAUSAL MECHANISM FOR CHILDHOOD LEUKEMIA DEVELOPING FROM -- AS A RESULT OF THE FETUS BEING EXPOSED TO CLASTOGENS, IS THAT SOMETHING DIFFERENT FROM TOPOISOMERASE II INHIBITION AND FLAVONOIDS?

MR. SCHURZ: OBJECTION; ASKED AND ANSWERED, UNINTELLIGIBLE, COMPOUND.

THE COURT: OVERRULED.

THE WITNESS: YES. AS I MENTIONED -- AS I TESTIFIED TO EARLIER TODAY, THERE ARE THREE BIOLOGICALLY PLAUSIBLE MECHANISMS BY WHICH CLASTOGENS WOULD PRODUCE CHROMOSOME DAMAGE IN THE FETUS AND MUTATIONS IN THE FETUS WHICH COULD LEAD TO LEUKEMIA.

THES INCLUDED CHROMOSOME BREAKS DIRECTLY FROM ACYRILAMIDE ACTING ON THE CHROMATIN; GLYCIDAMIDE BINDING TO THE DNA AND DAMAGING THE DNA; AND THE THIRD ONE WAS TOPOISOMERASE II INHIBITION, WHICH WOULD LEAD TO A VERY SPECIFIC TYPE OF INFANT LEUKEMIA WHICH OCCURRED IN THE FIRST YEAR OR TWO OF LIFE.

BUT IT'S MORE LIKELY THAT IN THE LATE -- OTHER TYPES OF CHILDHOOD LEUKEMIA, THAT THE GLYCIDAMIDE-INDUCED MUTATIONS AND THE ACYRILAMIDE DAMAGE TO THE
CHROMATIN, NOT THE TOPOISOMERASE II, ARE MORE IMPORTANT.

SO THESE THREE MECHANISMS COULD ALL WORK IN

CONCERT TO PRODUCE DIFFERENT FORMS OF CHILDHOOD

LEUKEMIA.

Q     BY MR. METZGER:  AS FAR AS THE MECHANISM

THAT YOU TESTIFIED IS GENERALLY ACCEPTED IN THE

SCIENTIFIC COMMUNITY FOR THE DEVELOPMENT OF CHILDHOOD

LEUKEMIA, WHICH OF THE THREE THAT YOU'VE JUST MENTIONED

IS IT?

A IT'S REALLY THE FIRST TWO:  THAT CHEMICALS

WOULD CROSS AND CAUSE DAMAGE TO THE DNA AND TO THE

PROTEINS INTERACTING WITH DNA, LEADING TO CHROMOSOME

TRANSLOCATIONS AND STRUCTURAL ABERRATIONS.  THE PART

ABOUT TOPOISOMERASE II, I AGREE, IS STILL A RESEARCH

ISSUE AND IS NOT FULLY ACCEPTED.

BUT IT IS ACCEPTED THAT CHROMOSOMAL CHANGES

ARISING FROM CHEMICAL EXPOSURES AND RADIATION EXPOSURES

IN UTERO ARE IMPORTANT IN THE DEVELOPMENT OF MOST FORMS

OF CHILDHOOD LEUKEMIA.

MR. METZGER:  THANK YOU VERY MUCH, PROFESSOR

SMITH.

THE COURT:  MAY THE WITNESS BE EXCUSED?

MR. SCHURZ:  YES, YOUR HONOR.

THE COURT:  DR. SMITH, YOU MAY STEP DOWN.  YOU MAY

BE EXCUSED.

WHAT'S THE LINEUP FOR THE NEXT WITNESS?

MR. METZGER:  I APOLOGIZE, YOUR HONOR.  THIS WENT

MUCH MORE QUICKLY THAN I ANTICIPATED.  I DON'T HAVE
ANOTHER WITNESS, BUT WE DO HAVE THE PMK TESTIMONY TO ADDRESS, AND WE CAN DO THAT.

THE COURT: THERE'S NO SENSE IN ARGUING ABOUT THAT. IS THERE AN ACTUAL PERSON WHO WILL TESTIFY AS A PMK?

MR. METZGER: WE HAVE THE EXCERPTS FOR YOU TO RULE ON, WITH THE OBJECTIONS.

MR. SCHURZ: THE ANSWER IS NO, WE HAVE NO PMK TESTIMONY IN PERSON THAT'S GOING TO BE OFFERED.

THE COURT: OKAY.

MR. METZGER: I'M SORRY. I DIDN'T --

THE COURT: SO YOU'RE TALKING ABOUT DEPOSITION TESTIMONY?

MR. METZGER: YES.

THE COURT: HAS THAT BEEN SUBMITTED ALREADY?

MR. METZGER: IT HAS BEEN, AND WE HAVE COPIES.

THE COURT: OKAY. AND SO IS PLAINTIFF READY TO REST?

MR. METZGER: NO, NO. OUR NEXT EXPERT IS DR. INFANTE, WHO IS ARRIVING ON MONDAY. YOU'RE DARK THURSDAY AND FRIDAY AND TOMORROW MORNING.

THE COURT: ALL RIGHT. SO LET'S JUST TAKE A LOOK AT THE SCHEDULE; LET'S GO OVER THE SCHEDULE.

SO HOW LONG IS THAT WITNESS GOING TO TESTIFY?

MR. METZGER: DR. INFANTE WILL BE EXTENSIVE. I'M ANTICIPATING HE'LL CONCLUDE SOME TIME ON WEDNESDAY, AT WHICH POINT WE WILL HAVE DR. HUFF HERE, READY TO GO.
THE COURT: AND HOW LONG IS HIS TESTIMONY?

MR. METZGER: I EXPECT THAT HE'LL FINISH BY FRIDAY. AND THEN THE FOLLOWING MONDAY, WE HAVE DR. BAYARD COMING. THEY'RE ALL COMING FROM THE EAST COAST.

THE COURT: 10-23. YOU'RE TALKING ABOUT 10-23 AND 10-24 FOR HUFF?

MR. METZGER: YES, THAT'S CORRECT. AND THEN DR. BAYARD WILL BE HERE TO TESTIFY ON THE 27TH, AND HE IS OUR LAST WITNESS.

THE COURT: OKAY. SO HOW LONG IS HIS TESTIMONY?

MR. METZGER: HE'S GOT TWO QUANTITATIVE CANCER RISK ASSESSMENTS. I WOULD ESTIMATE TWO TO THREE DAYS.

THE COURT: ALL RIGHT. 10-27 AND 28. AND THEN AFTER PLAINTIFF RESTS, ARE THERE GOING TO BE ANY REBUTTAL WITNESSES?

MR. SCHURZ: YES, YOUR HONOR. WE ANTICIPATE AT LEAST ONE REBUTTAL WITNESS THAT WE WILL BE PUTTING ON.

THE COURT: THAT WOULD BE APPROXIMATELY -- IS HE LOCAL OR AN OUT-OF-STATE WITNESS?

MR. SCHURZ: SHE'S OUT OF STATE.

THE COURT: SO THAT WOULD BE APPROXIMATELY OCTOBER 29TH THROUGH OCTOBER 30TH?

MR. SCHURZ: I WOULD THINK SO.

YOUR HONOR, WE WOULD -- I DON'T KNOW THAT I SHARE MR. METZGER'S ESTIMATES HERE WITH RESPECT TO EITHER DR. INFANTE TAKING THREE FULL DAYS OR --

THE COURT: I THINK IT'S VERY GENEROUS, THE TIME FRAME. BUT GO AHEAD.
MR. SCHURZ: AND I'M ABSOLUTELY CONFIDENT THAT DR. HUFF ISN'T GOING TO TAKE TWO DAYS. THERE'S --

THE COURT: WE WILL FINISH ALL THE TESTIMONY BY THE END OF OCTOBER. OKAY.

MR. SCHURZ: OKAY. I'M ADVISED THAT THE ANTICIPATED REBUTTAL EXPERT, DR. JULIE GOODMAN, IS AVAILABLE ON THE 3RD AND 4TH, WHICH WOULD BE INTO NOVEMBER -- MONDAY AND TUESDAY -- RATHER THAN THE 29TH.

THE COURT: IS SHE AVAILABLE EARLIER?

MR. SCHURZ: I WILL CHECK.

THE COURT: ALL RIGHT. WE'LL SEE HOW IT GOES.

LET'S SEE IF SHE CAN BE HERE EARLIER RATHER THAN STRETCH IT OUT FOR ANOTHER WEEK.

ALL RIGHT. SO ASIDE FROM THE PMK -- WHICH IS SUBMITTED, AND I CAN REVIEW IT IN CHAMBERS. I DON'T HAVE TO DO IT ON THE RECORD. I'LL PUT THE RULINGS ON THE RECORD.

DO WE HAVE A TRANSCRIPT THAT'S MARKED UP AS TO THE PORTIONS SOUGHT TO BE READ, AND THE OBJECTIONS?

MR. METZGER: WE DO, YOUR HONOR.

THE COURT: ALL RIGHT.

MR. METZGER: WE HAVE A PACKET FOR THE DIFFERENT WITNESSES.

THE COURT: ALL RIGHT. PLEASE SUBMIT THAT.

ALL RIGHT. SO THEN THE PLAN IS TO SEE EVERYONE --

MR. METZGER: WELL, YOUR HONOR --

THE COURT: YES.
MR. METZGER: -- THERE ARE TWO MATTERS I'D LIKE TO RAISE, IF I MIGHT.

THE COURT:  OKAY.

MR. METZGER: WE HAVE REQUESTS FOR JUDICIAL NOTICE, TWO REQUESTS FOR JUDICIAL NOTICE THAT WE --

THE COURT: WHY DON'T WE DO THAT AT 1:30, THEN.

MR. METZGER: OKAY.

THE COURT: UNLESS YOU WANT TO POSTPONE IT TILL MONDAY.

MR. METZGER: NO. 1:30 IS FINE.

THE COURT: DO YOU WANT TO COME BACK AT 1:30 THIS AFTERNOON OR DO THIS ON MONDAY?

MR. METZGER: I'M HAPPY TO COME BACK AT 1:30. I'D PREFER DOING IT NOW BECAUSE NEXT WEEK IS A BUSY WEEK.

THE COURT: A REQUEST FOR JUDICIAL NOTICE IS NOT GOING TO TAKE TOO LONG.

MR. SCHURZ: I WOULDN'T THINK SO. ALTHOUGH, YOUR HONOR, THEY HAVE FILED THINGS IN WRITING, AND WE WERE GOING TO RESPOND IN WRITING.

THE COURT: ALL RIGHT.

MR. SCHURZ: AND WE FILED ONE RESPONSE THIS MORNING. WE JUST RECEIVED THE OTHER ONE AND HAVE NOT PREPARED A RESPONSE TO THE OTHER, SO --

THE COURT: ALL RIGHT. SO HOW LONG BEFORE YOU HAVE YOUR WRITTEN RESPONSE?

MR. SCHURZ: I SUSPECT WE COULD HAVE IT IN TOMORROW, YOUR HONOR.

THE COURT: OKAY. ALL RIGHT. SO WE'LL POSTPONE
THE DISCUSSION ON THOSE REQUESTS FOR JUDICIAL NOTICE AND
OBJECTIONS UNTIL MONDAY, THE 20TH.

MR. SCHURZ: THANK YOU, YOUR HONOR.

THE COURT: 9:00 O'CLOCK.

ALL RIGHT. THANK YOU. HAVE A GOOD WEEK.

(AT 11:58 A.M., AN ADJOURNMENT WAS TAKEN
UNTIL MONDAY, OCTOBER 20, 2014, AT 9:00 A.M.)
EXHIBIT “D”
CURRICULUM VITAE

Martyn Thomas Smith, Ph.D.
Professor of Toxicology
Division of Environmental Health Sciences
School of Public Health
University of California
Berkeley, California  94720-7356

Phone: 510 -642-8770
Email: martynts@berkeley.edu

Birthplace:  Lincoln, England
Citizenship:  American

EDUCATIONAL BACKGROUND:

1977     B.Sc. (Honors) degree in Biology
         Queen Elizabeth College, University of London

1980     PhD in Biochemistry entitled "Studies on Oxidative Drug Metabolism Using Quantitative Cytochemical and
         Biochemical Methods."
         Department of Biochemistry and Chemistry,
         Medical College of St. Bartholomew's Hospital Charterhouse Square, London EC1M 6BQ

EMPLOYMENT HISTORY:

1980-1981  Post-doctoral researcher with Professor Sten Orrenius,
           Department of Toxicology.
           Karolinska Institute, Stockholm, Sweden

1981-1982  Teaching Fellow (Junior Lecturer) Toxicology Unit,
           Department of Pharmacology, School of Pharmacy,
           University of London

1981-1982  Taught the first combined BSc degree course in Toxicology and Pharmacology offered in the UK.

1982-present  Assistant Professor of Toxicology (1982-1987)
              Associate Professor of Toxicology (1987-1992)
              Professor of Toxicology (1992 - present)
              Currently Professor, Step IX.
              Division of Environmental Health Sciences
              School of Public Health,
              University of California, Berkeley

Appointments:

1986-2004  Associate Director, Health Effects Component of the UC Toxic Substances Program
1987-present  Director, NIEHS Superfund Basic Research Program
1988-2003  Staff Scientist, Lawrence Berkeley National Laboratory
1993-1994  Head, Division of Environmental Health Sciences
1994-1997  Deputy Head, Division of Environmental Health Sciences
1997-1998  Head, Division of Environmental Health Sciences
1998-2002  Deputy Head, Division of Environmental Health Sciences
2002-2004  Director, NIEHS Center for Environmental Health Sciences
2002-2005 Vice-Head, Division of Environmental Health Sciences
2008-2010 Vice-Head, Division of Environmental Health Sciences
2011-present Chair, Graduate Group in Molecular Toxicology.
2012-present Director, Berkeley Institute of the Environment

Awards and Honors:

Fellow of American Association for the Advancement of Science, 1994.
Visiting Professor, Chinese Academy of Preventive Medicine, Beijing, China, 1992.
Boehringer-Mannheim and Burroughs-Wellcome Post-doctoral Fellowships, 1980-81
Past-President, National Association of Superfund Research Program Directors (President 1995-97)
Distinguished Lecturer Award, National Cancer Institute, 2006
Certificate for Outstanding Service to the InterLymph Consortium, 2007
Distinguished Lecturer Award, Childrens Oncology Group, 2007
Children’s Environmental Health Network Award, 2010
Elected Fellow, Collegium Ramazzini, 2012
Alexander Hollaender Award, Environmental Mutagenesis and Genomics Society, 2014

UNIVERSITY AND PUBLIC SERVICE:

Directorship of Superfund Research Program

Dr. Smith has led the Superfund Basic Research Program at Berkeley since its inception. This program has been peer reviewed and renewed 5 times and is funded at approx. $2.5m per annum, making it the largest federal grant on the Berkeley campus. It has been audited several times because of its size and no problems have been encountered. It is widely considered one of the flagship programs for NIEHS. The goals of the UC Berkeley Superfund program are to improve understanding of the relationship between exposure and disease, provide better human and ecological risk assessments, and develop a range of prevention and remediation strategies to improve and protect public health, ecosystems and the environment. The program's themes are to: a) apply functional genomics, proteomics, transcriptomics, and nanotechnology to better detect arsenic, mercury, benzene, polycyclic aromatic hydrocarbons, trichloroethylene, and other Superfund priority chemicals in the environment; b) to evaluate their effects on human health, especially the health of susceptible populations such as children; c) remediate their presence; and d) reduce their toxicity. Currently 3 biomedical and 3 engineering projects are funded along with 4 cores.

Teaching Activities

Courses Taught

Advanced Toxicology (Toxicology 1) – PH270B, PH170B

Graduate Student Trainees

Theses Chaired

Moiré L. Robertson, “Induction of Micronuclei by Benzene Metabolites: Studies with Isolated Lymphocytes,” Ph.D. 1992. Currently Toxicologist at Variant, Walnut Creek, CA
Jean A. Grassman, “Development of an Immunoassay to Detect Benzene Adducts in Hemoglobin,” Ph.D. 1993, Associate Professor, Brooklyn College, City University of New York.


Joseph Wiemels, "Ras Oncogene Involvement in the Leukemic Phenotype and the Development of Mutational Biomarkers of Chemical Leukemogens,” Ph.D. 1997. Currently Associate Professor at UC San Francisco, Department of Epidemiology and Biostatistics.

Caroline Tanner, “The Relative Contributions of Genetic and Environmental Factors to the Cause of Parkinsons Disease,” Ph.D. 1998. Currently head of clinical research at Parkinson’s Institute, San Jose, CA.


Christine Skibola, “Polymorphisms in the Methyleneetetrahydrofolate Reductase Gene and Susceptibility to Acute Leukemia in Adults,” M.S. 1999; Ph.D. 2001. Currently Chair and Professor at University of Alabama, School of Public Health, Dept. of Epidemiology.


Christine Hegedus, “Applications of proteinchip array-based proteomics in molecular epidemiology and toxicology,” Ph.D. 2007; first student to graduate with doctoral degree in Toxicology from UC Berkeley. Currently a scientist at Amgen.


Selected Postdoctoral Trainees

Ann de Peyster, 1983-4, now Professor of Toxicology and Dean, School of Public Health, San Diego State University, San Diego, CA.

David Ross, 1985-6, now Professor and Chair of Molecular and Environmental Toxicology, University of Colorado, Denver, CO.

Donato DiMonte, 1986-7, now Head of Basic Research, Parkinson’s Institute, San Jose, CA.


Vangala Subrahmanyam, 1990-93, now VP and Head, Division of Drug Metabolism and Pharmacokinetics, SAI.

Jenny Quintana, 1990-1, Associate Professor, San Diego State University, San Diego, CA.

Immaculata de Vivo, 1993-5, Associate Professor of Epidemiology, Harvard University.

Jan Semenza, 1995-6, now Associate Professor of Molecular Epidemiology, Portland State University.

Michael Jeng, 1997-9, now Assistant Professor of Hematology at Stanford University.

Matthew Forrest, 2001-3, Senior Scientist, Assay Development, TwistDX Ltd, Cambridge UK.

Patricia Escobar-Stein, 2001-3, Principal Scientist, Boehringer-Ingelheim Pharmaceuticals, Andrew Olaharski, 2004-6, Assoc Director of Toxicology, Roche Pharmaceuticals, Palo Alto, CA.

Noé Galvan, 2004-6, Scientist, Clorox, Pleasanton, CA.

XuFeng Ren, 2007-2010, Assistant Professor, University of Buffalo, NY.


Recent service as an oral and thesis examiner for doctoral students

Cassandra Calloway, Qualifying Exam, 5/24/2004


Kevin Anthony Ford, Qualifying exam, 8/25/2005

Christopher Kaffer, Qualifying exam, 2005. Thesis committee 2007

Daniel Nomura, Chair, Qualifying exam, 2/8/2006

David Duberow, Qualifying exam, 3/7/2006

William Jo, Chair, Qualifying exam, 9/14/2006

Rachael Jones, Chair, Qualifying exam, 11/16/2006
Christine Keenan, Qualifying exam and thesis committee, 2007
William Jo, Thesis committee 2008
Daniel Nomura, Thesis committee 2008
Samantha Cronier, Qualifying exam, 10/10/2008
David Duberow, Thesis committee, 2009
Richard Novak, Qualifying exam and thesis committee, 2010-2013

Recent Service on University Committees
Member, Richmond Bay Campus committee, 2012
Member, Committee on Research, 2010-2011
Member, CAPRA, 2007-2010.
Vice-Chair, Graduate Council, 2006-7.
Member, Graduate Council, 2005-6.
Search committee, Faculty position in Environmental Health Sciences, 2005-6; Chair 2010-11.
Search committee, Faculty position in Nanotechnology and Environment, 2005-6.
Search committee, Faculty position in Nutritional Sciences and Toxicology, 2005-6.
Member, Campuswide Li Ka-Shing Building Committee, 2005-7.
Co-Chair of Committee to review Functional Genomics Facility at request of Vice-Chancellor, report produced 2005.
Member, Campus Committee on the Environment, 2002-4.
Chair, Faculty Council, School of Public Health, 2003-5.
Chair, Strategic Planning Committee, School of Public Health, 2002-3.
Member, Senate Committee on Research, 2000.
Member, Laboratory Operations and Safety Committee for the Campus, 1997-2000, 2001-3.
Member of Faculty Council, School of Public Health, 1999-2000, 2002-3.
Chair, Research Committee, School of Public Health, 1998-99.
Member, Hazardous Waste Management Committee for the Campus 1997-99.

PROFESSIONAL ACTIVITIES:

Recent Invited Lectures

2010


“Using Omics for Biomarker Discovery,” Invited speaker and co-organizer of Educational session at AACR Special meeting on Future of Molecular Cancer Epidemiology, Miami, FL, June 4, 2010.

“Dealing with the complexity of the environment through an exposomics approach”, Invited speaker and co-organizer, AACR Special meeting on Future of Molecular Cancer Epidemiology, Miami, FL, June 8, 2010.


“Benzene, Exposomics and the Future”, Invited speaker at Biological Reactive Intermediates VIII, Barcelona, Spain, July 18, 2010

"Using Omics to Assess Human Exposure", Invited seminar at Maastricht University, The Netherlands, September 28, 2010


2011


“Methodologies for analyzing the exposome – The Exposome Alliance”, Imperial College, University of London, March 9, 2011.


“Measuring the Exposome to Discover the Environmental Causes of Cancer”, AACR annual meeting, Orlando, FL, April 2, 2011.

“Characterizing the Exposome to Complement the Genome”, Special lecture at Human Genetics Foundation (HuGeF) in Turin, Italy, May 26, 2011.

“Characterizing the Exposome to Complement the Genome”, Plenary lecture at Annual meeting of the MRC-HPA Centre for Environment & Health, Imperial College, University of London, UK, June 9, 2011.

“Characterizing the Exposome to Complement the Genome”, Special lecture at Symposium, School of Pharmacy, University of Colorado, Denver, Co, September 15, 2011.

2012

“Characterizing the Exposome to Complement the Genome”, Department of Epidemiology Seminar, UCSF, March 2, 2012


“Characterizing the Human Exposome,” Keynote lecture introduced by Dr. L. Birnbaum at Aspen Cancer Conference, Aspen CO, July 2012.

““The Exposome Paradigm,” Chair and opening lecturer for session on the Exposome, Trans-NIH meeting on Inflammation and Aging in Disease, Bethesda, MD, September 5-7, 2012.

“The Exposome Paradigm,” Keynote speaker at meeting of NIEHS Center at Univ. of Washington, Seattle, WA, October 26, 2012.


2013


“Characterizing the Exposome to Complement the Genome”, Invited seminar at German Cancer Research Center, Heidelberg, Germany, July 12, 2013.

“Genome-Exposome Interactions in Leukaemia Aetiology”, Invited keynote speaker at UK Environmental Mutagenesis Society meeting, Bristol, UK, July 14-17, 2013


“Susceptibility to and Mechanisms of Benzene Toxicity”, Invited keynote lecture at the Brazilian Society of Toxicology meeting in Porto Alegre, Brazil, October 9, 2013

“Risk assessment for benzene”, Invited plenary lecture at the Brazilian Society of Toxicology meeting in Porto Alegre, Brazil, October 9, 2013.

“Characterizing the Exposome to Complement the Genome”, Invited seminar at Tsinghua University, Beijing China, November 4, 2013.

“Characterizing the Exposome to Complement the Genome”, Invited seminar at China Central Normal University, Wuhan, China, November 4, 2013.


Expert adviser to IARC at monograph meeting on Quantitative Risk Assessment, Lyon, France, November, 18-19, 2013.
Service to Editorial Boards of Scientific Journals

Member of the Editorial Board:
- Cancer Epidemiology, Biomarkers and Prevention (2007-present)
- Reviews in Mutation Research (2008-p)resent)
- Cell Biochemistry and Function (2008-present)

Prior member of Editorial Board of:
- Environmental Health Perspectives (2003 – 2008)
- Biomarkers (1995-2001)
- Molecular Toxicology
- International Journal of Toxicology
- Advances in Pharmacology

Recent reviewer for the following journals:
- Environmental Science and Technology
- Environmental Health Perspectives
- Cancer Research
- Chemical Research in Toxicology
- Toxicology
- Toxicology and Applied Pharmacology
- Biomarkers
- Carcinogenesis
- Leukemia
- Leukemia Research
- Hematologica
- Risk Analysis
- Mutation Research
- Environmental and Molecular Mutagenesis.

Membership of Advisory Boards

Elected Member of the Scientific Advisory Board of the International Agency for Research on Cancer, Lyon, France, 2010-2014.

Member of the Advisory Board to HuGeF, Turin, Italy, 2008-present

Member of the Advisory Board of the EU “Envirogenomarkers” project led by Prof. Soterios, Athens, Greece, 2008-present.

Member of the External Advisory Board of the Center for Environmental Health Sciences at Univ. of North Carolina, 2009-

Member of the Advisory Board for the MRC-HPA Centre for Environment & Health at the University of London, UK, 2009 - present.

Member of the Advisory Board for the MRC-NIHR National Phenome Centre, University of London, UK, 2012 -.

Professional Societies and Memberships

Local
- Genetic and Environmental Toxicology Association (GETA) of Northern California (President, 1987)
- Society of Toxicology, Northern California Chapter (NorCal SOT)
- (Founding member and chair of the Nominating Committee, 1986)

National
- American Association for Cancer Research (AACR)
- American Association for the Advancement of Science (AAAS)
- American Society of Hematology (ASH)
- Environmental Mutagen Society (EMS)
- Society of Toxicology (SOT)

Recent Service to Professional Societies

Elected member of the Molecular Epidemiology Group of the American Association for Cancer Research, Former Chair of Communications Committee.

Member of Program Committee for 2001, Annual Society of Toxicology Meeting in San Francisco, CA.
Member of Program Committee for 2001, Short Course Organizer and Invited Symposium Speaker at the 2001 Environmental Mutagen Society meeting in San Diego, California, March 16-21, 2001.
Member of the Program Planning Committees for the 2002 and 2003 Environmental Mutagen Society meetings in Anchorage, Alaska and Miami, FL.
Member of the Organizing committee for the AACR-SOT Special Conference on ‘Molecular and Genetic Epidemiology of Cancer’, Hawaii, January, 2003.
Member of the Program committee for the International Union of Toxicology (IUTOX) satellite meeting in Tampere, Finland July 2004.
Co-Chair of the Working Group on Predicting Chemical Carcinogenicity for 2006-8.
Member of the Program Planning Committee for the 2008 Environmental Mutagen Society meeting.
Member of Program Committee for 2010 AACR meeting.
Member of Organizing Committee of AACR special conference on the Future of Molecular Epidemiology, 2010.

Service to Educational and Government Agencies

Member of National Advisory Environmental Health Sciences Council, January 2000 - December 2003. This committee advises NIEHS, NIH on all actions.

Member of the National Leukemia/Brain Cancer Workshop Steering Committee for the National Cancer Institute.

Member of Committee on National Study of Myelodysplastic Syndromes, Office of Rare Diseases, National Heart, Lung and Blood Institute.

Ad hoc Member, XNDA Study Section, NIH, 2006-7.

Member, Strategic Planning Committee, NIEHS, 2011.

RESEARCH AND PUBLICATIONS:

Published Research Papers in Peer-Reviewed Journals


factor for hematologic malignancy, is associated with the NQO1 P609C->T mutation and rapid fractional excretion of chlorzoxazone. *Cancer Res*, 57(14):2839-42. PMID 9230185.


and Effector Memory T Cells, and CD8(+) Naïve T Cells, are Associated with Trichloroethylene Exposure. Front Oncol. 1:53. PMCID: PMC3355872.


**Edited Book**


**Other Published Work – Book chapters etc.**


Technical Reports


Book Reviews