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August 15, 2018

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

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

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

CERT'S SUBMISSION NO. 16

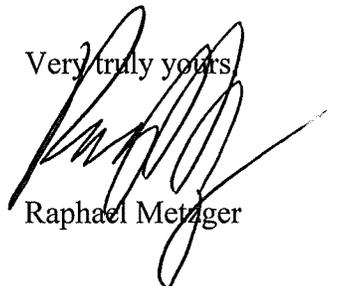
Dear Ms. Vela:

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:

1. Exhibit A - Opinions of Martyn T. Smith in CERT v. McDonald's (2007)
2. Exhibit B - Opinions of Martyn T. Smith in CERT v. Starbucks (2014)
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 acrylamide¹⁻⁵.
- 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^{8,63}.
- 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^{25,59,61,64-66}.
- 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.”

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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.”

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EXHIBIT “C”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT NO. 323

HON. ELIHU M. BERLE, JUDGE

COUNCIL FOR EDUCATION AND)
RESEARCH ON TOXICS,)

PLAINTIFF,)

VS.)

NO. BC435759

STARBUCKS CORPORATION,)
ET AL.,)

DEFENDANTS.)

AND CONSOLIDATED ACTION.)

REPORTER'S TRANSCRIPT OF TRIAL PROCEEDINGS

TUESDAY, OCTOBER 14, 2014

APPEARANCES:

FOR THE PLAINTIFF:

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CCROLA JOB
NO. 114671

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

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1 CASE NUMBER: BC435759
2 CASE NAME: CERT VS. STARBUCKS
3 DEPARTMENT: 323 HON. ELIHU M. BERLE
4 REPORTER: DANA SHELLEY, RPR, CSR #10177
5 LOS ANGELES, CALIFORNIA TUESDAY, OCTOBER 14, 2014
6 TIME: 9:19 A.M.
7 APPEARANCES: (AS HERETOFORE NOTED.)
8

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

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

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

15 THE COURT: PROFESSOR SMITH, PLEASE COME FORWARD.

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

18
19 MARTYN THOMAS SMITH,
20 CALLED AS A WITNESS BY THE PLAINTIFF, WAS SWORN AND
21 TESTIFIED AS FOLLOWS:

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

24 THE WITNESS: MY NAME IS MARTYN, M-A-R-T-Y-N,
25 THOMAS, T-H-O-M-A-S, SMITH, S-M-I-T-H.

26 THE CLERK: THANK YOU.

27 THE COURT: GOOD MORNING, PROFESSOR SMITH.

28 MR. METZGER, PLEASE PROCEED.

1 MR. METZGER: THANK YOU, YOUR HONOR.

2

3

DIRECT EXAMINATION

4 BY MR. METZGER:

5 Q GOOD MORNING, PROFESSOR SMITH.

6 A GOOD MORNING, MR. METZGER.

7 Q YOU ARE A PROFESSOR OF WHAT?

8 A I'M A PROFESSOR OF TOXICOLOGY AT THE
9 UNIVERSITY OF CALIFORNIA AT BERKELEY.

10 Q OKAY. HOW LONG HAVE YOU BEEN A PROFESSOR OF
11 TOXICOLOGY AT BERKELEY?

12 A 32 YEARS.

13 Q I'M GOING TO SHOW YOU WHAT'S BEEN MARKED AS
14 EXHIBIT 331. AND I'LL ASK YOU TO CONFIRM THAT THIS IS A
15 COPY OF YOUR CURRICULUM VITAE.

16 A IT IS.

17 (EXHIBIT 331 MARKED FOR IDENTIFICATION.)

18 Q BY MR. METZGER: OKAY. AND DOES IT SET
19 FORTH YOUR PROFESSIONAL QUALIFICATIONS, YOUR EDUCATION,
20 TRAINING, AND EXPERIENCE?

21 A IT DOES, AS OF APRIL OF THIS YEAR.

22 Q DOES IT ALSO INCLUDE A LIST OF YOUR
23 PUBLICATIONS?

24 A IT DOES.

25 Q NOW, DID YOU PREPARE A LIST OF OPINIONS FOR
26 THIS CASE REGARDING THE OPINIONS THAT YOU HAVE FORMED
27 REGARDING ACRYLAMIDE?

28 A I DID.

1 Q AND I'LL SHOW YOU WHAT'S BEEN MARKED AS
2 EXHIBIT 32. IS THAT THE LIST OF OPINIONS, WITH
3 REFERENCES -- SUPPORTING REFERENCES?

4 A IT IS.

5 (EXHIBIT 32 MARKED FOR IDENTIFICATION.)

6 MR. METZGER: YOUR HONOR, I WOULD OFFER THE
7 CURRICULUM VITAE, EXHIBIT 331, IN EVIDENCE.

8 THE COURT: ANY OBJECTION?

9 MR. SCHURZ: NO OBJECTION, YOUR HONOR.

10 THE COURT: ALL RIGHT. EXHIBIT 331 IS IN
11 EVIDENCE.

12 (EXHIBIT 331 RECEIVED IN EVIDENCE.)

13 Q BY MR. METZGER: AND HAVE YOU PREPARED A
14 POWERPOINT PRESENTATION TO FACILITATE THE RENDITION OF
15 YOUR TESTIMONY AT TRIAL?

16 A I HAVE.

17 Q IS THAT EXHIBIT 352?

18 A YES.

19 (EXHIBIT 352 MARKED FOR IDENTIFICATION.)

20 Q BY MR. METZGER: ALL RIGHT. HAVE YOU
21 DIRECTED A LABORATORY AT UC BERKELEY?

22 A YES. I DIRECT THE GENES AND ENVIRONMENT
23 LABORATORY, ALONG WITH PROFESSORS RAPPAPORT AND LUOPING
24 ZHANG.

25 Q AND WHAT IS THE GENES AND ENVIRONMENT
26 LABORATORY? WHAT DOES IT DO?

27 A IT AIMS TO UNDERSTAND THE INTERACTIONS
28 BETWEEN OUR GENES AND THE ENVIRONMENT AND ENVIRONMENTAL

1 EXPOSURES AND TO UNDERSTAND HOW TOXIC CHEMICALS ACT IN
2 THE HUMAN BODY.

3 Q HAVE YOU DIRECTED A SUPERFUND RESEARCH
4 PROGRAM AT UC BERKELEY?

5 A YES, SINCE 1986.

6 Q AND WHAT IS THAT PROGRAM?

7 A IT'S A PROGRAM TO STUDY THE HEALTH EFFECTS
8 OF TOXIC SUBSTANCES FOUND AT SUPERFUND SITES AND ALSO TO
9 DEVELOP METHODS FOR THEIR REMEDIATION AND TREATMENT.

10 Q WOULD YOU TELL US WHAT POSITIONS YOU'VE HELD
11 AT UC BERKELEY.

12 A I CAME AS AN ASSISTANT PROFESSOR OF
13 TOXICOLOGY IN 1982. I WAS PROMOTED TO TENURE IN 1987
14 AND THEN TO FULL PROFESSOR IN 1992. I'VE HELD VARIOUS
15 POSITIONS WITHIN THE UNIVERSITY, INCLUDING MOST RECENTLY
16 DIRECTOR OF THE BERKELEY INSTITUTE OF ENVIRONMENT.

17 I'VE ALSO SERVED ON THE GRADUATE COUNCIL AS
18 THE VICE CHAIR, WHICH OVERSEES ALL GRADUATE EDUCATION AT
19 BERKELEY. I'VE CHAIRED THE FACULTY OF THE SCHOOL OF
20 PUBLIC HEALTH.

21 AND I'VE SERVED AS HEAD OF MY DIVISION,
22 WHICH IS SOMETHING WE ROTATE AMONGST SENIOR COLLEAGUES.
23 AND I'VE BEEN DIRECTOR, AS YOU MENTIONED, OF THE
24 SUPERFUND RESEARCH PROGRAM AT BERKELEY -- WHICH IS THE
25 LARGEST FEDERAL GRANT ON THE CAMPUS -- FOR THE LAST 27
26 YEARS OR SO.

27 Q HOW LARGE IS THAT GRANT?

28 A IT'S \$2.5 MILLION PER YEAR. IT'S AUDITED

1 ALMOST EVERY YEAR BY THE FEDERAL GOVERNMENT BECAUSE OF
2 ITS SIZE, AND IT'S A LARGE -- TAKES A LOT OF MY TIME TO
3 MANAGE SUCH A GRANT.

4 Q OKAY. YOU MENTIONED YOUR DIVISION. WHAT
5 DIVISION IS THAT?

6 A IT'S THE DIVISION OF ENVIRONMENTAL HEALTH
7 SCIENCES, WITHIN THE SCHOOL OF PUBLIC HEALTH.

8 Q OKAY. HAVE YOU SEEN A BIOGRAPHICAL SUMMARY
9 OF YOU THAT HAS BEEN POSTED ON THE UC WEBSITE?

10 A I HAVE.

11 Q AND DOES THAT INCLUDE A DESCRIPTION OF YOUR
12 RESEARCH INTERESTS?

13 A IT DOES.

14 Q ALL RIGHT. I HAVE TAKEN THE LIBERTY OF
15 BULLET-POINTING THOSE. I'D LIKE TO GO OVER THEM WITH
16 YOU.

17 BIOMARKERS OF CARCINOGENESIS. WOULD YOU
18 TELL US WHAT THAT IS AND WHAT YOUR RESEARCH IN THAT AREA
19 HAS BEEN.

20 A CARCINOGENESIS IS THE DEVELOPMENT OF CANCER
21 IN LIVING ORGANISMS, INCLUDING HUMANS. AND WE WOULD
22 LIKE TO OBTAIN BIOMARKERS, WHERE WE TAKE A SAMPLE OF
23 BLOOD OR SOME OTHER EASILY ACCESSIBLE TISSUE, AND
24 PREDICT WHO IS GOING TO GET CANCER. THAT'S WHAT THE
25 FIRST AREA IS ABOUT.

26 Q AND HOW LONG HAS THAT BEEN A RESEARCH
27 INTEREST OF YOURS?

28 A FOR OVER 20 YEARS.

1 Q THE NEXT ONE IS DIET AS A RISK FACTOR FOR
2 CANCER. TELL US ABOUT THAT, PLEASE.

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

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

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

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

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

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

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

1 THE CAUSE OF THE CHILDHOOD LEUKEMIA.

2 AND WITH PATRICIA BUFFLER, I BEGAN A LARGE
3 STUDY IN CALIFORNIA OF CHILDHOOD LEUKEMIA THAT BEGAN IN
4 1995, THROUGH THE SUPERFUND PROGRAM. WE'VE BEEN
5 EXAMINING MANY DIFFERENT TYPES OF ENVIRONMENTAL EXPOSURE
6 IN RELATION TO THE INCIDENCE OF CHILDHOOD LEUKEMIA IN
7 CALIFORNIA.

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

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

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

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

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

28 Q DOES THE BIOGRAPHICAL SUMMARY ON THE UC

1 BERKELEY WEBSITE ALSO INCLUDE A DESCRIPTION OF YOUR
2 EXPERTISE?

3 A YES.

4 Q OKAY. IT SAYS:

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

15 IS THAT A FAIR DESCRIPTION OF YOUR FIELDS OF
16 EXPERTISE?

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

20 THE COURT: OVERRULED.

21 YOU CAN ANSWER THE QUESTION.

22 THE WITNESS: YES, IT IS.

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

26 A SURE. WELL, I GREW UP IN NORTHERN ENGLAND
27 AND WENT TO THE UNIVERSITY OF LONDON TO DO A DEGREE IN
28 BIOLOGY, HAVING DECIDED NOT TO DO MEDICINE, AND BECAME

1 INTERESTED IN DOING RESEARCH THERE.

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

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

12 THERE WAS NOT MUCH AVAILABILITY OF TRAINING
13 IN TOXICOLOGY IN ENGLAND AT THAT TIME, SO I WENT TO
14 SWEDEN TO WORK AT THE KAROLINSKA INSTITUTE, WHICH GIVES
15 OUT NOBEL PRIZES; AND WORKED WITH STEN ORRENIUS, WHO WAS
16 CONSIDERED PROBABLY THE BEST TOXICOLOGIST IN THE WORLD
17 AT THE TIME, AND DID POSTDOCTORAL RESEARCH WITH HIM IN
18 1980 TO '81.

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

21 A I DO.

22 Q WILL YOU TELL US ABOUT YOUR TEACHING
23 ACTIVITIES.

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

28 SINCE THAT TIME, I'VE CONSISTENTLY TAUGHT AT

1 BERKELEY. WE TEACH A LARGE CLASS TO FRESHMAN AND
2 SOPHOMORES, INTRODUCING THEM TO THE SUBJECT OF
3 TOXICOLOGY. THIS CLASS VARIES BETWEEN 200 AND 400
4 STUDENTS EVERY YEAR.

5 I'VE ALSO TAUGHT FOR MANY YEARS NOW THE MAIN
6 CLASS, THE CORE CLASS, IN TOXICOLOGY TO GRADUATE
7 STUDENTS IN OUR PROGRAM.

8 Q WOULD YOU TELL THE COURT ABOUT SOME OF THE
9 ADVISORY POSITIONS THAT YOU'VE HELD.

10 A I MOST RECENTLY SERVED, FOR EXAMPLE, ON THE
11 SCIENTIFIC COUNCIL OF THE INTERNATIONAL AGENCY FOR
12 RESEARCH ON CANCER. I WAS THE ELECTED REPRESENTATIVE
13 FROM THE UNITED STATES ON THAT COUNCIL, WHICH OVERSEES
14 ALL SCIENCE MATTERS AT IARC, AS IT'S CALLED.

15 I'VE ALSO SERVED ON THE BOARDS OF VARIOUS
16 EUROPEAN ORGANIZATIONS AND U.S. CENTERS, AND I'VE ACTED
17 AS AN ADVISOR TO MANY GOVERNMENTS ON THE ISSUE OF
18 BENZENE.

19 I'VE ALSO SERVED ON THE NATIONAL ADVISORY
20 ENVIRONMENTAL HEALTH SCIENCES COUNCIL, WHICH ADVISES THE
21 NIH ON ALL THE AREAS RELATED TO ENVIRONMENTAL HEALTH.

22 Q WOULD YOU TELL US ABOUT SOME OF THE ELECTED
23 POSITIONS THAT YOU'VE HAD IN PROFESSIONAL SOCIETIES.

24 A WITH PROFESSIONAL SOCIETIES, I'VE ACTED WITH
25 THE MOLECULAR EPIDEMIOLOGY GROUP OF THE AMERICAN
26 ASSOCIATION FOR CANCER RESEARCH. I HAVE SERVED ON
27 VARIOUS ADVISORY BOARDS TO LARGE INSTITUTIONS AND
28 CENTERS.

1 Q AND WOULD YOU TELL THE COURT BRIEFLY ABOUT
2 SOME OF THE AWARDS AND HONORS THAT YOU'VE RECEIVED OVER
3 THE YEARS.

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

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

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

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

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

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

1 A YES.

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

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

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

11 Q ALL RIGHT. LET'S TALK ABOUT ACRYLAMIDE.
12 WOULD YOU TELL THE COURT WHAT I ASKED YOU TO EVALUATE
13 FOR THIS CASE REGARDING ACRYLAMIDE.

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

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

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

24 Q WHAT IS THE SIGNIFICANCE OF THAT?

25 MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT, UNDER
26 EVIDENCE CODE 352, AS DUPLICATIVE AND REDUNDANT. DR.
27 RAPPAPORT TESTIFIED ABOUT THIS TOPIC AT SOME LENGTH.
28 DR. MELNICK TESTIFIED ABOUT THIS AT SOME LENGTH. THE

1 EXACT SLIDE THAT WE'RE LOOKING AT HERE WAS IN
2 RAPPAPORT'S SLIDES AT NO. 22.

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

5 THE COURT: MR. METZGER?

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

10 THE COURT: OKAY.

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

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

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

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

25 A NO. I WAS SURPRISED TO SEE THAT HE SAID
26 THAT. IT'S NOT A REACTIVE OXYGEN SPECIES. IT'S AN
27 ACTIVATED MOLECULE WITH OXYGEN INSERTED INTO IT, BUT IT
28 IS NOT WHAT WE CLASSICALLY CALL A REACTIVE OXYGEN

1 SPECIES.

2 MR. METZGER: ALL RIGHT.

3 (PAUSE IN PROCEEDINGS.)

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

6 Q ALL RIGHT. HAVE YOU PUBLISHED REGARDING
7 ACRYLAMIDE?

8 A YES, WE HAVE.

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

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

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

15 A IT IS.

16 Q WHAT DID YOU INVESTIGATE IN THAT STUDY?

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

24 AND SO THIS -- THESE EXPERIMENTS SHOWED THAT
25 IF YOU EXPOSE THE FATHER TO ACRYLAMIDE AND THEN MATE
26 THAT MALE MOUSE WITH A FEMALE MOUSE, THE GENETIC DAMAGE
27 IN THE MALE IS PASSED ALONG TO THE EMBRYO; WHICH IS
28 QUITE UNUSUAL AND SHOWS HOW AGGRESSIVE ACRYLAMIDE IS AT

1 PRODUCING GENETIC DAMAGE IN THE SPERM OF MALES.

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

8 AND SO THIS IS WHAT THIS PAPER SHOWED.

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

13 THE COURT: OBJECTION OVERRULED.

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

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

21 Q WOULD YOU EXPLAIN TO THE COURT WHAT
22 MICRONUCLEI ARE.

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

27 IF THE CHROMOSOMES ARE DAMAGED DURING THAT
28 PROCESS, IT'S POSSIBLE TO FORM SMALL INDIVIDUAL TINY

1 LITTLE NUCLEI, THAT WE CALL MICRONUCLEI, WHICH CONTAIN
2 FRAGMENTS OF DNA WHICH SHOULD NORMALLY BE IN THE
3 NUCLEUS.

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

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

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

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

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

26 Q OKAY.

27 A SO IT SHOWS AGAIN THAT EXPOSURE OF THE
28 FATHER WILL LEAD TO EFFECTS IN THE EMBRYO.

1 Q AND WHAT, FROM THESE STUDIES THAT YOU DID,
2 RELATES TO ACRYLAMIDE AND CANCER, IF ANYTHING?

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

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

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

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

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

23 THE COURT: PURE ACRYLAMIDE?

24 THE WITNESS: YES.

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

27 THE WITNESS: IT PROBABLY IS IN A LIQUID FORM AS
28 WE ADMINISTER IT, BUT IT'S NOT MIXED WITH ANYTHING ELSE.

1 THE COURT: THE EXTENT OF DILUTION, DOES THAT
2 AFFECT IT AT ALL?

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

5 THE COURT: THANK YOU.

6 COUNSEL.

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

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

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

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

20 Q WHAT IS CLASTOGENICITY?

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

25 CLASTOGENICITY IS ONE FORM OF GENOTOXICITY,
26 WHICH -- IT REFERS TO THE BREAKAGE OF CHROMOSOMES, WHERE
27 THE STRANDS OF THE DNA HAVE BEEN BROKEN, AND THE
28 CHROMOSOMES ARE FRAGMENTED IN SOME FASHION.

1 Q WHAT IS THE TOXICOLOGICAL SIGNIFICANCE OF A
2 CHEMICAL BEING A CLASTOGEN?

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

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

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

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

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

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

27 AND WHEN THEY DID THAT, THEY FOUND THAT
28 THOSE WHO HAD A HIGH LEVEL OF CHROMOSOME ABERRATIONS 20

1 TO 30 YEARS BEFORE DEVELOPING CANCER WERE AT HIGHER RISK
2 OF DEVELOPING THOSE CANCERS -- THINGS LIKE LUNG CANCER,
3 LEUKEMIAS, OTHER THINGS -- THAN THE GENERAL -- THOSE
4 WITH A LOWER LEVEL.

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

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

13 Q WHAT IS THE SIGNIFICANCE OF THAT TO YOU?

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

20 Q WILL YOU TELL THE COURT SPECIFICALLY WHAT
21 YOU MEAN BY "CHROMOSOME ABERRATIONS." WHAT DAMAGE ARE
22 YOU TALKING ABOUT?

23 A WHAT I'M TALKING ABOUT IS, IF YOU LOOK UNDER
24 A MICROSCOPE, THE CHROMOSOMES SHOULD ALL BE ALIGNED AND
25 BE THE RIGHT SIZE, AND THERE SHOULD BE 46 OF THEM, AND
26 THEY SHOULD ALL LOOK INTACT.

27 IF THERE ARE CHROMOSOME ABERRATIONS, THERE
28 WILL BE CHANGES TO THOSE STRUCTURES. THERE WILL BE BITS

1 BROKEN OFF, BITS LOST, SHORTER CHROMOSOME; MAYBE A WHOLE
2 CHROMOSOME LOST, MAYBE ANOTHER ONE GAINED. THERE WILL
3 BE CLEAR DIFFERENCES.

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

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

13 A SO IT'S NOW BEEN ESTABLISHED THAT
14 MICRONUCLEI ARE ALSO PREDICTIVE OF FUTURE CANCER RISK.

15 GIVEN THE SUCCESS OF THE STUDY WITH
16 CHROMOSOME ABERRATIONS, AN INTERNATIONAL GROUP OF
17 RESEARCHERS GOT TOGETHER, POOLED ALL OF THEIR DATA ON
18 MICRONUCLEI, AND LOOKED AT WHO DEVELOPED CANCER IN THESE
19 DIFFERENT COUNTRIES -- EVERYWHERE FROM SWEDEN, TO
20 AUSTRALIA, TO THE UNITED STATES.

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

25 Q AND THESE ARE STUDIES IN PEOPLE?

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

28 Q ALL RIGHT. HAVE YOU PUBLISHED REGARDING THE

1 CLASTOGENICITY OF CHEMICALS TO HUMANS?

2 A YES. SO ONE OF THE MECHANISMS BY WHICH
3 BENZENE IS THOUGHT TO CAUSE LEUKEMIA IS THROUGH A
4 CLASTOGENIC MECHANISM. AND THE SAME IS TRUE FOR
5 IONIZING RADIATION AND FOR CANCER CHEMOTHERAPY DRUGS.

6 THE WAY THAT THEY ARE THOUGHT TO CAUSE
7 LEUKEMIA IS MAINLY THROUGH A CLASTOGENIC CHROMOSOME-
8 BREAKING MECHANISM.

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

11 A SO WE HAVE DONE STUDIES IN CELL CULTURE
12 WHERE WE TOOK HUMAN CELLS FROM HUMAN BLOOD, AND WE TOOK
13 STEM CELLS FROM CORD BLOOD. AND WE'VE EXPOSED THEM TO
14 VARIOUS METABOLITES OF BENZENE, INCLUDING HYDROQUINONE
15 AND CATECHOL. AND I HAVE SEEN INCREASED LEVELS OF
16 CHROMOSOME BREAKS, OR CLASTOGENICITY, IN THOSE CELLS.

17 WE'VE ALSO LOOKED AT PEOPLE EXPOSED TO
18 BENZENE IN THE WORKPLACE AND HAVE SIMILARLY FOUND
19 INCREASED LEVELS OF CHROMOSOME BREAKAGE IN THOSE
20 INDIVIDUALS.

21 Q WHAT IS THE SIGNIFICANCE OF THAT RESEARCH TO
22 YOU?

23 A THIS SUGGESTS OR INDICATES THAT ONE OF THE
24 PROBABLE MECHANISMS BY WHICH BENZENE PRODUCES LEUKEMIA
25 IS THROUGH A CLASTOGENIC CHROMOSOME-BREAKING MECHANISM,
26 DAMAGING STEM CELLS AND BLOOD CELLS IN THE BONE MARROW
27 AND IN THE BLOOD; AND THAT THIS LEADS TO SUBSEQUENT
28 DEVELOPMENT OF CANCERS LIKE LEUKEMIA.

1 Q ALL RIGHT. DR. RAPPAPORT INFORMED THE COURT
2 THAT THE TOXICOKINETIC PROCESSES OF ACRYLAMIDE WERE ALL
3 LINEAR, BUT HE DIDN'T TALK ABOUT CLASTOGENICITY,
4 SPECIFICALLY, I DON'T BELIEVE.

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

7 A YES. THE STUDIES THAT HAVE BEEN --

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

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

15 THE COURT: MR. METZGER?

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

21 THE COURT: ALL RIGHT. OBJECTION OVERRULED FOR
22 NOW.

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

25 A NO. COULD WE DO IT AGAIN?

26 Q SURE. IS CLASTOGENICITY ALSO A LINEAR
27 PROCESS?

28 A IN THE STUDIES THAT HAVE BEEN DONE -- WHERE

1 THEY'VE BEEN ABLE TO EXAMINE CLASTOGENICITY USING WHAT
2 WE CALL A FLOW CYTOMETER, A VERY SENSITIVE MACHINE, DOWN
3 TO VERY LOW LEVELS -- IT'S BEEN SHOWN THAT OVER A LARGE
4 DOSE RANGE, CLASTOGENS ACT IN A LINEAR FASHION,
5 INCLUDING ACRYLAMIDE.

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

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

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

20 THE COURT: OVERRULED.

21 MR. METZGER: ALL RIGHT.

22 Q PROFESSOR SMITH, IS ACRYLAMIDE CLASTOGENIC?

23 A YES.

24 Q AND HOW DO YOU KNOW THAT?

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

1 METHODOLOGIES.

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

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

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

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

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

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

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

27 A THAT ACRYLAMIDE IS CLEARLY GENOTOXIC. IT
28 CLEARLY IS ABLE TO GET -- BE CONVERTED TO A METABOLITE

1 THAT BINDS TO DNA AND DAMAGES DNA, IS DNA REACTIVE. SO
2 IT'S ABLE TO PRODUCE POINT MUTATIONS THROUGH ITS
3 GLYCIDAMIDE.

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

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

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

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

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

25 THERE ARE EFFECTS IN EXPERIMENTAL ANIMALS
26 WHERE RADIO-LABELED ACRYLAMIDE HAS BEEN SHOWN TO CROSS
27 INTO THE FETUS AND THAT THE LEVELS IN THE FETUS ARE VERY
28 SIMILAR TO THE LEVELS IN THE BLOOD OF THE MOTHER.

1 SO THERE'S BEEN MEASUREMENTS OF ADDITION
2 PRODUCTS -- CALLED ADDUCTS -- IN THE FETUS AND IN THE
3 CORD BLOOD, COMPARED TO THE MOTHER; AND AGAIN, VERY
4 SIMILAR LEVELS SHOWN.

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

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

9 A NO.

10 Q HOW DO YOU KNOW THAT?

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

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

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

23 THE COURT: MR. METZGER?

24 MR. METZGER: MAY I LAY A FOUNDATION?

25 THE COURT: YES.

26 MR. METZGER: ALL RIGHT.

27 Q PROFESSOR SMITH, HAVE YOU READ THE EUROPEAN
28 FOOD SAFETY AUTHORITY REPORT TITLED "DRAFT SCIENTIFIC

1 OPINION ON ACRYLAMIDE IN FOOD"?

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

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

5 A IT WAS.

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

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

12 THE COURT: OBJECTION SUSTAINED.

13 MR. METZGER: OKAY.

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

18 A YES.

19 Q WHAT DO THEY MEAN?

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

27 PREGNANT WOMEN ARE CLEARLY A POPULATION
28 THAT'S CONSIDERED TO BE A SUSCEPTIBLE POPULATION.

1 Q WHY ARE UNBORN CHILDREN SUSCEPTIBLE
2 POPULATIONS?

3 A BECAUSE THEY ARE DEVELOPING. THEY ARE
4 GROWING VERY QUICKLY. CELLS ARE DIVIDING AND CHANGING.
5 THE FETUS IS CLEARLY BECOMING A HUMAN BEING. AND THAT
6 PROCESS IS VERY SENSITIVE TO INTERFERENCE BY OUTSIDE
7 INFLUENCES, SUCH AS TOXIC CHEMICALS.

8 Q ARE INFANTS ALSO A SENSITIVE POPULATION?

9 A INFANTS ARE ALSO A SENSITIVE POPULATION
10 BECAUSE THEY'RE VERY SMALL FOR THE AMOUNT OF AIR THAT
11 THEY BREATHE IN AND THE AMOUNT OF FOOD AND WATER THAT
12 THEY TAKE IN.

13 SO CLEARLY, THE EXPOSURE OF THEIR TISSUES TO
14 A PARTICULAR CHEMICAL COULD BE MUCH HIGHER THAN THAT IN
15 AN ADULT MALE, FOR EXAMPLE. AND SO, AGAIN, THEY'RE
16 CONSIDERED TO BE A SENSITIVE POPULATION.

17 Q ARE SENSITIVE POPULATIONS, IN YOUR OPINION,
18 SOMETHING THAT A RISK ASSESSOR SHOULD CONSIDER?

19 A YES. THEY'RE WELL -- THESE FACTORS ARE WELL
20 UNDERSTOOD BY RISK ASSESSORS, AND THERE ARE GUIDELINES
21 TO INCLUDE ADDITIONAL SAFETY FACTORS IF PREGNANT WOMEN
22 OR YOUNG CHILDREN ARE EXPOSED.

23 Q HAVE YOU READ PUBLICATIONS OF THE WORLD
24 HEALTH ORGANIZATION REGARDING ACRYLAMIDE?

25 A I HAVE. AND THE WORLD HEALTH ORGANIZATION
26 WERE ONE OF THE FIRST TO MAKE COMMENTS ABOUT ACRYLAMIDE,
27 FOLLOWING ITS DISCOVERY IN FOOD IN 2002.

28 Q DO YOU AGREE WITH THE CONCLUSION OF THE

1 WORLD HEALTH ORGANIZATION THAT THE PRESENCE OF
2 ACRYLAMIDE IN FOOD IS A MAJOR CONCERN IN HUMANS, BASED
3 ON THE ABILITY TO INDUCE CANCER AND HERITABLE MUTATIONS
4 IN LABORATORY ANIMALS?

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

7 THE COURT: OVERRULED.

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

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

15 A I DO.

16 Q WHY?

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

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

27 Q ALL RIGHT. LET'S CHANGE TOPICS AND TALK
28 ABOUT COFFEE.

1 A OKAY.

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

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

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

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

17 THE COURT: THE SLIDES ARE NOT IN EVIDENCE.
18 OBJECTION OVERRULED.

19 MR. METZGER: OKAY.

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

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

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

1 SPECIES WHICH CAN DAMAGE THE DNA.

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

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

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

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

16 HE WROTE AN ARTICLE CALLED "PESTICIDES ARE
17 99.9 PERCENT NATURAL." AND IN THAT ARTICLE, IN THE
18 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, HE
19 BASICALLY DESCRIBED MANY OF THE CLASTOGENIC-TYPE
20 MOLECULES THAT WERE PRESENT IN VARIOUS FOODSTUFFS,
21 INCLUDING COFFEE.

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

26 SO HE AND I HAD A LOT OF DEBATES ABOUT THIS
27 TOPIC, AND IT'S WHEN I FIRST BECAME AWARE. IT WAS
28 PROBABLY IN 1986, OR SOMETHING LIKE THAT.

1 Q OKAY. YOU MENTIONED EARLIER HYDROQUINONE
2 AND CATECHOL, I BELIEVE, AS METABOLITES OF BENZENE.

3 A YES.

4 Q ARE THOSE CLASTOGENIC CHEMICALS?

5 A YES. IF YOU ADD THOSE TO CELLS, THEY BREAK
6 THE CHROMOSOMES OF THE CELLS.

7 Q AND ARE THOSE PRESENT IN COFFEE?

8 A YES.

9 Q I THINK YOU MENTIONED THAT BENZENE IS
10 METABOLIZED BY THE CYP2E1 ENZYME; IS THAT CORRECT?

11 A THAT'S CORRECT.

12 Q IS THAT THE SAME METABOLIC ENZYME BY WHICH
13 ACRYLAMIDE IS METABOLIZED TO GLYCIDAMIDE?

14 A IT IS.

15 Q AND WHAT IS THE SIGNIFICANCE OF THAT?

16 A WELL, THE SIGNIFICANCE IS THAT BASICALLY THE
17 SAME RISK FACTORS THAT -- AND THE SENSITIVITY FOR
18 BENZENE WILL APPLY TO ACRYLAMIDE ALSO.

19 Q OKAY. PROFESSOR SMITH, HAVE YOU AUTHORED
20 ARTICLES IN THE PEER-REVIEWED LITERATURE REGARDING THE
21 RELATIONSHIP BETWEEN CHEMICALS THAT AFFECT TOPOISOMERASE
22 II AND THE DEVELOPMENT OF LEUKEMIA?

23 A YES. SO ONE OF THE MECHANISMS BY WHICH
24 HYDROQUINONE AND CATECHOL AND OTHER METABOLITES OF
25 BENZENE ARE THOUGHT TO CAUSE LEUKEMIA IS THROUGH THE
26 INHIBITION OF TOPOISOMERASE II.

27 AND SO WE HAVE, SINCE THE MID 1990S, WITH MY
28 GRADUATE STUDENT DAVID EASTMAN -- WHO IS NOW A PROFESSOR

1 AT UC RIVERSIDE -- HAVE LOOKED AT THE ROLE OF
2 TOPOISOMERASE II INHIBITION AND LEUKEMIA INDUCED BY
3 BENZENE AND ITS METABOLITES.

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

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

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

10 A THAT THE INHIBITION OF TOPOISOMERASE II CAN
11 OCCUR IN HUMANS EXPOSED TO BENZENE. IT'S BEEN PROVEN BY
12 DAVID EASTMAN'S GROUP THAT IT OCCURS IN EXPERIMENTAL
13 ANIMALS, IN BONE MARROW, FOLLOWING EXPOSURE TO BENZENE;

14 AND THAT IT'S WIDELY CONSIDERED AND
15 GENERALLY ACCEPTED THAT INHIBITION OF TOPOISOMERASE II
16 IS A RISK FACTOR FOR FUTURE DEVELOPMENT OF LEUKEMIA.

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

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

25 A YES.

26 Q IS THAT IT?

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

1 COMPLICATED.

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

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

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

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

18 Q UNTANGLING?

19 A YES.

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

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

28 AND SO WHAT THE TOPOISOMERASE DOES IS JUST

1 BASICALLY MAKES SURE THAT THE DNA DOESN'T GET TANGLED AS
2 YOU UNTANGLE THE BALL OF WOOL. THAT'S WHY EVERY CELL,
3 FROM BACTERIA ON, HAS IT.

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

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

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

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

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

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

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

25 SO YOU CUT AND REJOIN WITHIN THE ENZYME.

26 Q OKAY.

27 A THIS ALSO MEANS THAT IF YOU INHIBIT THE
28 ENZYME OR DAMAGE IT IN SOME WAY, THAT THAT BREAK COULD

1 NOT BE REPAIRED. AND THIS IS A WAY OF GETTING BREAKS
2 WITHIN THE DNA.

3 Q OKAY. I THINK WE DO HAVE A GRAPHIC WHICH
4 SHOWS -- WELL, TELL US -- EXPLAIN TO THE COURT WHAT THIS
5 SHOWS.

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

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

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

17 Q AND THIS ONE ENZYME DOES ALL THOSE THINGS?

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

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

25 A YES. ACRYLAMIDE WILL INHIBIT TOPOISOMERASE
26 II. AND SO WILL SOME OF THE OTHER -- SUCH AS
27 CHLOROGENIC ACID, THAT I MENTIONED EARLIER, AND
28 HYDROXYHYDROQUINONE, WHICH ARE PRESENT IN COFFEE -- WILL

1 ALSO DAMAGE TOPOISOMERASE II AND INHIBIT ITS NORMAL
2 ACTIVITY.

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

5 A I HAVE.

6 Q APPROXIMATELY HOW MANY ARTICLES?

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

10 MR. METZGER: YOUR HONOR, MAY WE?

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

13 (RECESS.)

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

16 PROFESSOR SMITH IS ON THE STAND.

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

19 THE WITNESS: I DO.

20 THE COURT: PLEASE STATE YOUR NAME FOR THE RECORD.

21 THE WITNESS: MY NAME IS MARTYN THOMAS SMITH.

22 THE COURT: THANK YOU.

23 MR. METZGER IS INQUIRING.

24 MR. METZGER: THANK YOU, YOUR HONOR.

25 THE COURT: COUNSEL, YOU MAY PROCEED.

26 Q BY MR. METZGER: PROFESSOR SMITH, BEFORE THE
27 BREAK, WE WERE -- YOU WERE TELLING THE COURT ABOUT
28 TOPOISOMERASE INHIBITORS AND LEUKEMIA.

1 WOULD YOU EXPLAIN TO THE COURT WHAT CHEMICAL
2 TOPOISOMERASE INHIBITORS HAVE BEEN SHOWN TO BE INVOLVED
3 IN THE DEVELOPMENT OF LEUKEMIA, AND EXPLAIN WHY.

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

8 Q SO --

9 A AND --

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

13 A CORRECT.

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

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

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

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

28 Q WHAT IS A SECONDARY LEUKEMIA?

1 A IT'S A LEUKEMIA ARISING AFTER ANOTHER
2 CANCER, SO SECONDARY TO TREATMENT WITH A CANCER DRUG.

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

5 A CORRECT.

6 Q OKAY. AND WHAT IS SUCH A DRUG?

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

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

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

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

26 SO THE FIRST SUGGESTION OF THIS CAME FROM
27 JULIE ROSS'S WORK, WHERE SHE STUDIED POTENTIAL INTAKE OF
28 TOPOISOMERASE II INHIBITORS FROM DIET AND ITS

1 ASSOCIATION WITH AN EARLY FORM OF CHILDHOOD LEUKEMIA
2 CALLED INFANT LEUKEMIA, WHICH OCCURS WITHIN THE FIRST
3 YEAR OR TWO OF LIFE.

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

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

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

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

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

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

23 Q CHROMOSOME 11?

24 A CHROMOSOME 11.

25 AND SO PEOPLE EXPOSED CELLS IN CULTURE TO
26 VARIOUS CHEMICALS WHICH THEY THOUGHT WOULD BE
27 TOPOISOMERASE II INHIBITORS, INCLUDING SOME CHEMICALS
28 FOUND IN SOY AND -- OTHER CHEMICALS FOUND IN SOY, SUCH

1 AS GENISTEIN, G-E-N-I-S-T-E-I-N, THAT WOULD DAMAGE THIS
2 PARTICULAR AREA OF CHROMOSOME 11.

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

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

14 Q ALL RIGHT. THANK YOU.

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

18 A YES.

19 Q AND WHAT IS YOUR OPINION?

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

23 AND THE MOST PROBABLE MECHANISM TO EXPLAIN
24 THIS IS THAT THE CLASTOGENIC CHEMICALS WITHIN COFFEE,
25 INCLUDING ACRYLAMIDE, CROSS INTO THE FETUS AND CAUSE
26 GENETIC DAMAGE IN THE FETUS OF THE TYPE WHERE THERE'S
27 CHROMOSOME BREAKAGE, WHICH LEADS TO CHROMOSOME
28 TRANSLOCATIONS, WHICH THEN DEVELOPS INTO LEUKEMIA.

1 Q INTO CHILDHOOD LEUKEMIA?

2 A CORRECT.

3 Q OKAY. LET'S FIRST -- BEFORE WE GET INTO THE
4 SPECIFICS OF THAT, I'D LIKE TO REVIEW SOME OF YOUR OWN
5 RESEARCH PUBLICATIONS REGARDING CHROMOSOME DAMAGE AND
6 CHILDHOOD LEUKEMIA.

7 LET ME JUST ASK YOU: IS ONE OF THE ARTICLES
8 THAT YOU AUTHORED AN ARTICLE TITLED "PRENATAL ORIGIN OF
9 CHILDHOOD ACUTE MYELOID LEUKEMIAS HARBORING CHROMOSOMAL
10 REARRANGEMENTS T(15; 17) AND INVERSION(16)"?

11 A YES.

12 Q AND WOULD YOU TELL THE COURT WHAT YOU DID IN
13 THAT STUDY AND WHAT YOU CONCLUDED.

14 A OKAY. SO WE HAVE COLLECTED, WITH PATRICIA
15 BUFFLER, MORE THAN 1,000 CASES OF CHILDHOOD LEUKEMIA IN
16 NORTHERN CALIFORNIA, AND WE HAVE CHARACTERIZED THE
17 CHROMOSOME CHANGES THAT ARE PRESENT WITHIN THEM.

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

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

1 WHERE PART OF THE CHROMOSOME IS SPUN AROUND.

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

5 Q WHAT WAS THE PURPOSE OF THAT?

6 A SO WE COULD THEN SEE WHETHER THE DISEASE WAS
7 PRESENT AT BIRTH.

8 Q OKAY.

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

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

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

22 Q OKAY.

23 A SO IT BEGINS WITHIN THE FETUS.

24 Q AS CHROMOSOME DAMAGE?

25 A AS CHROMOSOME DAMAGE.

26 Q OKAY. ANOTHER ARTICLE THAT YOU AND YOUR
27 COLLEAGUES WROTE IS TITLED "PRENATAL ORIGIN OF
28 CHROMOSOMAL TRANSLOCATIONS IN ACUTE CHILDHOOD LEUKEMIA:

1 IMPLICATIONS AND FUTURE DIRECTIONS." WILL YOU TELL THE
2 COURT WHAT THAT ARTICLE IS ABOUT.

3 A WELL, THAT ARTICLE BASICALLY USED THE
4 FINDINGS THAT WERE MOSTLY FROM OUR GROUP IN CALIFORNIA
5 AND A GROUP IN LONDON LED BY MEL GREAVES, WHICH
6 BASICALLY IDENTIFIED A WHOLE SERIES OF CHROMOSOMAL
7 CHANGES WHICH WOULD OCCUR BEFORE A CHILD IS BORN WHICH
8 COULD LEAD TO CHILDHOOD LEUKEMIA.

9 ONE OF THE ISSUES WITH THIS WAS THEN, WELL,
10 CAN YOU THEN PREDICT WHO IS GOING TO GET CHILDHOOD
11 LEUKEMIA BY A TEST AT BIRTH?

12 AND THE PROBLEM WITH THAT IS THAT THESE
13 CHROMOSOME CHANGES ARE PRESENT IN A LARGE NUMBER OF
14 CHILDREN, ONLY 1 PERCENT OF WHICH WILL GO ON TO DEVELOP
15 LEUKEMIA.

16 AND SO IT'S NOT A GOOD ENOUGH TEST IN TERMS
17 OF PREDICTION OF WHO WILL GET LEUKEMIA, BUT IT DOES SHOW
18 THAT -- FOR A PARTICULAR PATIENT, WHEN THEIR LEUKEMIA
19 BEGAN.

20 Q OKAY. YOU ALSO HAVE AN ARTICLE TITLED
21 "MOLECULAR BIOMARKERS FOR THE STUDY OF CHILDHOOD
22 LEUKEMIA." TELL THE COURT WHAT THAT'S ABOUT.

23 A THAT, AGAIN, IS ABOUT A REVIEW OF THIS TYPE
24 OF ISSUE AND ALSO ABOUT SOME OF THE WORK WE DID LOOKING
25 FOR PEOPLE WHO WOULD BE SUSCEPTIBLE -- GENETICALLY
26 SUSCEPTIBLE TO CHILDHOOD LEUKEMIA.

27 Q PROFESSOR SMITH, HAVE YOU FORMED AN OPINION
28 AS TO WHETHER IT IS GENERALLY ACCEPTED IN THE SCIENTIFIC

1 COMMUNITY THAT CHILDHOOD LEUKEMIA DEVELOPS IN UTERO FROM
2 CHROMOSOMAL CHANGES IN THE FETUS WHICH LEAD TO THE --
3 EVENTUALLY, TO THE DEVELOPMENT OF LEUKEMIA IN INFANTS
4 AND CHILDREN?

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

9 THE COURT: MR. METZGER, LAY A FOUNDATION.

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

13 A I DO.

14 Q WOULD YOU TELL US ABOUT THOSE.

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

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

23 AND FOR EXAMPLE, I RECENTLY PARTICIPATED AS
24 AN INVITED DISCUSSANT AND PRESENTER OF A WEBINAR
25 PRODUCED BY THE CENTERS FOR DISEASE CONTROL, WITH THE
26 AIM OF LOOKING AT WAYS TO PREVENT CHILDHOOD CANCER,
27 WHERE I SPOKE ABOUT BENZENE AS A CAUSE OF CHILDHOOD
28 CANCER.

1 AND I AM IN REGULAR TOUCH WITH ALL THE
2 LEADING RESEARCHERS IN THE WORLD ON THIS TOPIC.

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

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

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

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

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

22 LACKS FOUNDATION.

23 THE COURT: OVERRULED.

24 THE WITNESS MAY ANSWER THE QUESTION.

25 THE WITNESS: THE GENERAL CONSENSUS IN THE
26 SCIENTIFIC COMMUNITY IS THAT CHROMOSOME CHANGES ARISING
27 IN UTERO ARE A MAJOR CAUSE OF CHILDHOOD LEUKEMIA; AND
28 THAT THERE ARE EXCEPTIONS, BUT IN GENERAL, MOST

1 CHILDHOOD LEUKEMIAS OCCUR -- ARISE FROM A PROCESS THAT
2 BEGINS IN THE FETUS.

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

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

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

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

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

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

28 Q ALL RIGHT. WHEN YOU SAY THIS COULD OCCUR,

1 IS THERE EVIDENCE THAT IT DOES OCCUR?

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

5 Q AND WHAT IS THAT EVIDENCE?

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

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

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

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

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

26 AND SUBSEQUENTLY, A META-ANALYSIS OF ALL OF
27 THESE STUDIES CONCLUDED THAT THERE WAS AN ASSOCIATION
28 BETWEEN HIGH INTAKE OF COFFEE AND SUBSEQUENT RISK OF

1 CHILDHOOD LEUKEMIA. AND THE INVESTIGATORS CALLED FOR
2 FURTHER STUDY OF THIS IN LARGE INTERNATIONAL COHORTS.

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

5 ALL OF THE STUDIES THAT DR. SMITH JUST
6 REFERENCED WERE DISCUSSED AT SOME LENGTH BY DR. MELNICK.
7 SO WE'VE NOW HEARD FROM TWO EXPERTS WITH RESPECT TO THE
8 SAME SET OF STUDIES AND THEIR ANALYSIS OF THOSE STUDIES.
9 I SUSPECT THAT WE'RE GOING TO HEAR FROM YET ANOTHER IN
10 THE FORM OF DR. PETER INFANTE.

11 SO WE WOULD MOVE TO STRIKE DR. SMITH'S
12 TESTIMONY AS REDUNDANT AND DUPLICATIVE, UNDER 352.

13 THE COURT: THE OBJECTION IS OVERRULED.

14 NEXT QUESTION.

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

21 A YES, I HAVE.

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

25 AND THE IDEA THAT CHEMICALS FROM COFFEE
26 COULD CROSS THE PLACENTA INTO THE FETUS AND PRODUCE
27 CHROMOSOME DAMAGE OF THE TYPE FOUND IN CHILDHOOD
28 LEUKEMIA ADDS WEIGHT TO THE CONCEPT THAT COFFEE -- HIGH

1 INTAKE OF COFFEE CAN PRODUCE CHILDHOOD LEUKEMIA, BECAUSE
2 OF IT BEING BIOLOGICALLY PLAUSIBLE.

3 Q WHAT IS IT ABOUT THE BIOLOGICAL PLAUSIBILITY
4 OF, SPECIFICALLY, CLASTOGENS IN COFFEE THAT IS
5 BIOLOGICALLY PLAUSIBLE?

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

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

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

22 DOES THAT -- DO THOSE STUDIES SUPPORT YOUR
23 OPINION?

24 A WELL, THEY DO.

25 MR. SCHURZ: OBJECTION; LEADING.

26 THE COURT: SUSTAINED.

27 Q BY MR. METZGER: WOULD YOU TELL THE COURT,
28 WHAT ABOUT THOSE STUDIES IS SIGNIFICANT TO YOU IN YOUR

1 ASSESSMENT OF THIS ISSUE?

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

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

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

13 Q OKAY.

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

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

19 A IT DOES.

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

22 A THEY DO.

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

25 A YES.

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

28 A YES.

1 Q AND HOW DO YOU KEEP UP ON THAT?

2 A THERE'S ALL SORTS OF MECHANISMS THESE DAYS:
3 THROUGH RESEARCHGATE, LINKEDIN, AND VARIOUS WEBSITES
4 LIKE THAT. PLUS, WE REGULARLY SEARCH THE PUBMED
5 LITERATURE AND HAVE ALERTS SENT TO US ABOUT PARTICULAR
6 TOPICS.

7 Q OKAY. ARE YOU AWARE OF ANY STUDY THAT
8 CLAIMS TO HAVE DISPROVED THE MECHANISM OF CHILDHOOD
9 LEUKEMIA FROM CLASTOGENS CAUSING CHROMOSOME DAMAGE?

10 A NO.

11 Q NOW, IS THIS MECHANISM THAT YOU HAVE
12 DESCRIBED AS BEING GENERALLY -- WELL, THAT MECHANISM, I
13 UNDERSTAND -- IS IT YOUR TESTIMONY THAT MECHANISM IS
14 GENERALLY ACCEPTED?

15 A YES.

16 MR. SCHURZ: OBJECT, AND -- INTERPOSE AN OBJECTION
17 AS TO WHAT IS -- VAGUE AND AMBIGUOUS AS TO "MECHANISM";
18 AND AGAIN, LACKS FOUNDATION AS TO THIS WITNESS'S --

19 THE COURT: SUSTAINED.

20 Q BY MR. METZGER: WOULD YOU CLEARLY DEFINE
21 FOR US THE MECHANISM OF CHILDHOOD LEUKEMOGENESIS THAT
22 YOU CONSIDER TO BE GENERALLY ACCEPTED IN THE SCIENTIFIC
23 COMMUNITY.

24 A THE GENERALLY ACCEPTED MECHANISM IS THAT
25 WITHIN THE FETUS, CHROMOSOME DAMAGE OCCURS WITHIN THE
26 STEM CELLS OF EITHER THE LIVER OR THE BONE MARROW; AND
27 THAT THESE GENETIC CHANGES, THESE CHROMOSOMAL CHANGES,
28 ARE RETAINED AT BIRTH;

1 AND THAT CERTAIN -- THE SECOND -- AS THE
2 CHILD IS BORN AND THE IMMUNE SYSTEM DEVELOPS, THE
3 THINKING THEN IS THAT THESE CELLS CAN EITHER DIE OUT,
4 AND THE CHILD DOES NOT GET LEUKEMIA;

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

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

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

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

26 Q AND ARE THOSE CHANGES THAT YOU'VE JUST
27 DESCRIBED THE CHANGES THAT ARE CAUSED BY CHEMICAL
28 CLASTOGENS?

1 A THAT COULD BE ONE CAUSE. IT'S ALSO POSSIBLE
2 THAT THEY COULD ARISE JUST BY RANDOM ERRORS IN THE CELL.
3 BUT IT'S MUCH MORE LIKELY THAT THEY'RE CAUSED BY
4 CHEMICAL AGENTS OR RADIATION, WHICH WOULD PRODUCE VERY
5 SIMILAR CHANGES IN THE CHILDREN'S CELLS.

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

10 A NO, NOT AT ALL.

11 Q WOULD YOU EXPLAIN.

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

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

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

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

26 A A CHEMICAL THAT'S CONSIDERED TO BE A
27 TRANSPLACENTAL CARCINOGEN IS A CHEMICAL THAT WILL CROSS
28 FROM THE MOTHER INTO THE FETUS AND CAUSE DAMAGE, WHICH

1 THEN, ONCE THE FETUS IS BORN AND BECOMES A VIABLE
2 PERSON -- AS THEY GROW, THEY CAN DEVELOP CANCER.

3 AND SO IT'S THE PRODUCTION OF CANCER IN THE
4 OFFSPRING OF SOMEONE.

5 Q IN TRANSPLACENTAL CARCINOGENESIS, DOES
6 CANCER ACTUALLY MANIFEST IN THE FETUS?

7 A NO. TYPICALLY, LATER IN LIFE.

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

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

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

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

25 A YES. SO THEY -- IN THEIR GUIDELINES FOR
26 RISK ASSESSMENT FOR DEVELOPMENTAL TOXICANTS, THEY
27 REALIZED THAT SOME DEVELOPMENTAL TOXICANTS -- SOME
28 CHEMICALS WHICH WOULD CAUSE BIRTH DEFECTS AND THESE

1 TYPES OF EVENTS, THESE ADVERSE EVENTS, COULD ALSO
2 POTENTIALLY CAUSE CANCER IN THE OFFSPRING.

3 Q I'D LIKE TO SHOW YOU WHAT'S BEEN MARKED AS
4 EXHIBIT 351, A DOCUMENT ENTITLED "GUIDELINES FOR
5 DEVELOPMENTAL TOXICITY RISK ASSESSMENT OF THE U.S. EPA."

6 IS THIS WHAT YOU ARE REFERRING TO?

7 A YES.

8 (EXHIBIT 351 MARKED FOR IDENTIFICATION.)

9 Q BY MR. METZGER: ALL RIGHT. AND IS THERE A
10 PARTICULAR STATEMENT IN THIS GUIDELINE PREPARED BY THE
11 EPA REGARDING HOW TRANSPLACENTAL -- THE RISK OF
12 TRANSPLACENTAL CARCINOGENESIS SHOULD BE ASSESSED?

13 A YES. IT SAYS THAT --

14 Q WHERE ARE YOU, PLEASE?

15 A I'M SORRY. ON PAGE 5, THERE'S AN INFORMED
16 STATEMENT.

17 Q AND WOULD YOU READ THAT, PLEASE.

18 A SO IT'S --

19 MR. SCHURZ: I'LL OBJECT AS HEARSAY. WE'RE NOT
20 HERE TO HAVE THE WITNESS READ INTO THE RECORD --

21 THE COURT: OBJECTION SUSTAINED.

22 MR. METZGER: ALL RIGHT. YOUR HONOR, I WOULD
23 REQUEST JUDICIAL NOTICE OF EXHIBIT 351. IT'S AN EPA
24 CANCER -- IT'S AN EPA GUIDELINE THAT'S RELEVANT TO THIS
25 MATTER.

26 THE COURT: ANY OBJECTION?

27 MR. SCHURZ: YES, YOUR HONOR. WE WOULD OBSERVE,
28 THIS IS THE SUBJECT OF A WRITTEN MOTION, OR A REQUEST

1 FOR JUDICIAL NOTICE. WE INTEND TO OPPOSE THAT. IT'S
2 NOT CLEAR WHY THIS IS BEING PROVIDED TO US ON OCTOBER
3 THE 14TH, WHEN THESE THINGS WERE ALL DUE ON AUGUST THE
4 1ST.

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

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

11 NEXT.

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

16 A I DO.

17 Q AND WHAT IS YOUR BASIS FOR THAT OPINION?

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

26 MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT AND MOVE
27 TO STRIKE AS AN UNDISCLOSED OPINION, AS EVIDENCED BY THE
28 FACT THAT WE'RE SEEING THIS DOCUMENT IN OCTOBER. THIS

1 IS NOT PART OF DR. SMITH'S ORIGINAL SET OF OPINIONS, IT
2 WAS NOT THE SUBJECT OF HIS DEPOSITION TESTIMONY, AND
3 THIS IS THE FIRST TIME WE'RE HEARING IT.

4 THE COURT: ALL RIGHT. MR. METZGER?

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

8 THE COURT: ALL RIGHT. WE'LL ARGUE THAT LATER.
9 YOU CAN RENEW YOUR MOTION TO STRIKE LATER. AT THIS
10 TIME, THE COURT WILL ALLOW IT.

11 NEXT QUESTION.

12 Q BY MR. METZGER: ALL RIGHT. PROFESSOR
13 SMITH, WOULD YOU TELL THE COURT YOUR CONCLUSIONS AS TO
14 WHETHER ACRYLAMIDE PRESENTS A RISK OF CANCER TO INFANTS
15 AND CHILDREN FROM TRANSPLACENTAL EXPOSURE.

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

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

26 MR. SCHURZ: OBJECTION; LEADING.

27 THE COURT: OVERRULED.

28 THE WITNESS: YES. SO THERE ARE MULTIPLE ANIMAL

1 STUDIES THAT I'VE ALREADY MENTIONED THAT HAVE LED THE
2 IARC AND NTP AND THE EPA AND ALL AUTHORITATIVE BODIES TO
3 CONCLUDE THAT ACRYLAMIDE IS A PROBABLE HUMAN CARCINOGEN.

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

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

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

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

19 I HAVE NO FURTHER QUESTIONS AT THIS TIME.

20 THE COURT: ALL RIGHT. THANK YOU.

21 MR. SCHURZ.

22
23 CROSS-EXAMINATION

24 BY MR. SCHURZ:

25 Q GOOD MORNING, DR. SMITH.

26 A GOOD MORNING.

27 Q NOW, EARLIER, IN YOUR DISCUSSION WITH MR.
28 METZGER, YOU TESTIFIED THAT ACRYLAMIDE IS DISTRIBUTED TO

1 THE FETUS; IS THAT CORRECT?

2 A CORRECT.

3 Q AND NONE OF THE STUDIES THAT YOU HAVE LOOKED
4 AT AND PROVIDED AS PART OF YOUR RELIANCE MATERIALS HAVE
5 DETECTED ACTUAL DNA ADDUCTS FOR ACRYLAMIDE OR
6 GLYCIDAMIDE IN THE HUMAN PLACENTA; CORRECT?

7 A I DON'T THINK THAT'S BEEN EXAMINED, NO.

8 Q AND IN FACT, IN THE ANOLA (PHONETIC) STUDY,
9 WHICH YOU DID REVIEW, THE AUTHORS REPORTED LOOKING FOR
10 BUT NOT FINDING ACRYLAMIDE- AND GLYCIDAMIDE-DNA ADDUCTS
11 IN PLACENTAL TISSUE; CORRECT?

12 A I DON'T RECALL. I'D HAVE TO LOOK AT THAT
13 STUDY.

14 Q ALL RIGHT. YOU EARLIER TESTIFIED WITH
15 RESPECT TO FLAVONOIDS ACTING AS CLASTOGENS. DO YOU
16 RECALL THAT TESTIMONY?

17 A YES.

18 Q AND YOU'VE WRITTEN ON THE ISSUE OF
19 FLAVENOIDS, HAVE YOU NOT?

20 A I HAVE.

21 Q AND IN A 2000 ARTICLE THAT YOU PREPARED WITH
22 CHRISTINE SKIBOLA, YOU CONCLUDED THAT THE LEVEL OF
23 FLAVENOIDS REQUIRED TO INDUCE MUTATIONS AND CYTOTOXICITY
24 MAY NOT BE PHYSIOLOGICALLY ACHIEVABLE THROUGH DIETARY
25 SOURCES, DID YOU NOT?

26 A I DID.

27 Q AND WHAT YOU WERE LOOKING AT WITH FLAVENOIDS
28 IS THE POTENTIAL IMPACT OF WHAT YOU REFERRED TO AS

1 EXCESSIVE FLAVONOID INTAKE; CORRECT?

2 A YES.

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

5 A THAT'S CORRECT.

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

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

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

19 A CORRECT.

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

24 A CORRECT.

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

28 A THAT'S CORRECT.

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

5 A YES.

6 (EXHIBIT 1847 MARKED FOR
7 IDENTIFICATION.)

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

10 A YES.

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

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

16 A SHE DOES.

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

19 A CORRECT.

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

22 A YES.

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

25 A CORRECT.

26 Q ALL RIGHT. NOW, THE HYPOTHESIS THAT WAS
27 TESTED BY DR. ROSS IS THAT CONSUMPTION OF THESE FOODS
28 THAT CONTAIN TOPOISOMERASE II INHIBITORS MAY BE

1 ASSOCIATED WITH AN INCREASED RISK OF CHILDHOOD LEUKEMIA
2 IN THE OFFSPRING; CORRECT?

3 A CORRECT.

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

7 A SHE DID, YES.

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

11 A I DO.

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

16 A YES.

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

19 A YES.

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

25 A NO.

26 Q AND HAS ANY GOVERNMENT AGENCY ADVISED
27 PREGNANT WOMEN NOT TO EAT BEANS DURING PREGNANCY BECAUSE
28 IT MAY LEAD TO AN INCREASED RISK OF CHILDHOOD LEUKEMIA

1 IN THEIR OFFSPRING?

2 A NO.

3 Q LET'S TURN NOW TO --

4 THANK YOU. NOTHING FURTHER WITH RESPECT TO
5 THIS EXHIBIT.

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

9 A CORRECT.

10 Q AND YOU CITED THE SPECTOR INVESTIGATION;
11 CORRECT?

12 A CORRECT.

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

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

18 Q ALL RIGHT. THAT WAS MY NEXT QUESTION.

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

22 A NO.

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

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

28 A IT'S THE ARTICLE BY LOGAN SPECTOR AND

1 OTHERS, PUBLISHED IN 2005.

2 (EXHIBIT 1980 MARKED FOR
3 IDENTIFICATION.)

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

6 A I DID.

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

9 A I DID.

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

13 A CORRECT.

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

16 A IT DOES.

17 Q NOW, LET'S TAKE A LOOK -- IF I CAN DIRECT
18 YOUR ATTENTION TO TABLE NO. 3, AT PAGE 0004 OF EXHIBIT
19 1980. AND DO YOU HAVE THAT IN FRONT OF YOU?

20 A I DO.

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

27 A CORRECT.

28 Q AND IN THIS CONTEXT, UNLIKE THE PRIOR STUDY,

1 WHAT THEY FOUND WAS, IN LOOKING AT THE TOPOISOMERASE II
2 FOODS -- THAT THEY'VE IDENTIFIED AS THE VF-PLUS INDEX.
3 DO YOU SEE THAT?

4 A YES.

5 Q AND THE "VF-PLUS INDEX" REFERS TO VEGETABLES
6 AND FRUIT PLUS OTHER TOPOISOMERASE II-CONTAINING --
7 INHIBITOR-CONTAINING FOODS; CORRECT?

8 A CORRECT.

9 Q ALL RIGHT. AND WITH RESPECT TO THESE
10 VALUES, WHAT THE AUTHORS FOUND WAS THE ABSENCE OF ANY
11 INCREASED ASSOCIATION OR INCREASED RISK OF ACUTE
12 LEUKEMIA AND INCREASING CONSUMPTION OF THE FRUITS-AND-
13 VEGETABLES-PLUS INDEX; CORRECT?

14 A YES.

15 Q IN FACT, WHAT THEY FOUND IN CERTAIN CASES
16 WAS A STATISTICALLY SIGNIFICANT DECREASED RISK, DID THEY
17 NOT?

18 A WELL, IT'S MARGINAL WITH REGARDS TO -- YES.
19 AT THE TOP, IT'S STATISTICALLY SIGNIFICANT TO MLL PLUS,
20 YES.

21 Q ALL RIGHT. AND THE AUTHORS DID NOT FIND ANY
22 STATISTICALLY SIGNIFICANT INCREASE ASSOCIATED WITH
23 EITHER OF THE DNA-TOPOISOMERASE II-INHIBITOR FOOD
24 INDICES THEY CREATED; CORRECT?

25 A WHAT THEY DID FIND WAS A CONFIRMATION OF
26 THEIR EARLIER STUDY, WHICH WAS THAT THE MLL PLUS AML,
27 THERE WAS A SIGNIFICANTLY INCREASED RISK.

28 Q WAS IT STATISTICALLY SIGNIFICANT?

1 A WELL, IT'S 3.2-FOLD. I AGREE, IT'S NOT
2 STATISTICALLY SIGNIFICANT, AND THE TREND IS MARGINAL;
3 BUT IT'S A VERY, VERY SMALL NUMBER OF CASES.

4 Q THANK YOU, DR. SMITH.

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

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

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

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

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

20 A I DID NOT.

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

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

27 (EXHIBIT 1907 MARKED FOR
28 IDENTIFICATION.)

1 Q BY MR. SCHURZ: SO THAT WAS MY NEXT
2 QUESTION. IS THIS -- DID YOU RELY ON THIS PAPER IN
3 FORMING YOUR OPINIONS?

4 A YES.

5 Q ALL RIGHT. AND THIS PAPER IS TITLED
6 "ACRYLAMIDE CATALYTICALLY INHIBITS TOPOISOMERASE II IN
7 V79 CELLS"; CORRECT?

8 A CORRECT.

9 Q NOW, THERE ARE GENERALLY RECOGNIZED TO BE
10 TWO CATEGORIES OF TOPOISOMERASE II INHIBITORS, ARE THERE
11 NOT?

12 A YES.

13 Q AND ONE SUCH CATEGORY IS A TOPOISOMERASE II
14 POISON; CORRECT?

15 A CORRECT.

16 Q AND THE SECOND CATEGORY WOULD BE A
17 TOPOISOMERASE II CATALYTIC INHIBITOR; CORRECT?

18 A CORRECT.

19 Q AND AS OUTLINED HERE IN THE SCIANDRELLO
20 PAPER, ACRYLAMIDE IS A -- IS OF THAT SECOND CATEGORY:
21 IT IS A CATALYTIC INHIBITOR; CORRECT?

22 A CORRECT.

23 Q AND THAT, MOREOVER, ACRYLAMIDE DOES NOT ACT
24 AS A TOPOISOMERASE II POISON; CORRECT?

25 A CORRECT.

26 Q ALL RIGHT. NOW, LET'S DISCUSS FOR A MOMENT
27 THE SIGNIFICANCE OF THAT CATEGORY. AND LET ME SHOW YOU
28 NOW ANOTHER ARTICLE THAT WAS PART OF YOUR PRODUCTION.

1 I'M SHOWING YOU EXHIBIT 1468, AN ARTICLE BY
2 MIGUEL LOPEZ-LAZARO FROM 2011. AND CAN YOU IDENTIFY
3 THIS DOCUMENT FOR US.

4 A AS YOU JUST MENTIONED.

5 (EXHIBIT 1468 MARKED FOR
6 IDENTIFICATION.)

7 Q BY MR. SCHURZ: AND DID YOU RELY ON THIS
8 DOCUMENT -- WELL, STRIKE THAT.

9 DID YOU REVIEW THIS DOCUMENT?

10 A I BELIEVE SO, YES.

11 Q AND DID YOU RELY ON THIS DOCUMENT IN FORMING
12 YOUR OPINIONS IN THIS CASE?

13 A NOT STRONGLY, NO.

14 Q ALL RIGHT. WE DID OBSERVE THAT IT WAS CITED
15 IN YOUR MATERIALS. IS IT THE CASE THAT YOU DID NOT RELY
16 ON THIS DOCUMENT IN FORMING YOUR OPINIONS IN THIS CASE?

17 A IT'S NOT NECESSARY TO MY OPINIONS.

18 Q ALL RIGHT. WELL, LET'S TALK FOR A MOMENT,
19 THEN, WITH RESPECT TO THE CONSEQUENCE OF THE CATEGORIES
20 THAT WE'VE BEEN DISCUSSING: TOPO 2 POISONS AND TOPO 2
21 CATALYTIC INHIBITORS.

22 LET'S START WITH CATALYTIC INHIBITORS. NOW,
23 IS IT THE CASE THAT CATALYTIC INHIBITORS ARE GENERALLY
24 ASSOCIATED WITH CELL DEATH; IS THAT CORRECT?

25 A THERE IS SOME DEBATE ABOUT THAT, AND THERE
26 IS ALSO DEBATE ABOUT THE MISCLASSIFICATION OF CATALYTIC
27 VERSUS POISON.

28 NEIL OSHEROFF NOW BELIEVES THAT ALL OF THESE

1 ARE ALL POISONS WORKING ON DIFFERENT SITES WITHIN THE
2 TOPOISOMERASE II AND THAT THE SEPARATION OF THE
3 CATALYTIC AND POISONS IS SOMEWHAT ARTIFICIAL;

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

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

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

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

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

27 A NO, I DON'T BELIEVE SO. WHAT THEY WILL DO
28 IS PREVENT THE POISONS FROM BINDING TO THE PROTEIN AND

1 THEREFORE ACTING. SO THEY PREVENT THE THINGS LIKE THE
2 PODOPHYLLOTOXINS FROM ACTING ON THE TOPO II. BUT THEY
3 ALL -- ALL THE CATALYTIC INHIBITORS WILL ALSO PRODUCE
4 STRAND BREAKS AND BREAK THE DNA.

5 Q ALL RIGHT. BUT THESE CATALYTIC INHIBITORS,
6 AS REPORTED BY LOPEZ-LAZARO, WILL ACTUALLY ACT TO
7 ANTAGONIZE CERTAIN TOPOISOMERASE II POISONS; IS THAT
8 CORRECT?

9 A THEY'LL ANTAGONIZE THEM, YES.

10 Q OKAY. NOW, WE LOOKED AT, EARLIER, SLIDE
11 NO. 35, THAT WAS INCLUDED IN YOUR PRODUCTION. AND IF WE
12 COULD TAKE A LOOK AT THAT NOW. IT WAS ENTITLED
13 "CONCURRENCE WITH THE WHO."

14 AND YOU INDICATED THAT YOU HAVE -- THAT YOU
15 CONCUR WITH THE RECOMMENDATION OF THE WORLD HEALTH
16 ORGANIZATION, AS ARTICULATED HERE; CORRECT?

17 A I CONCUR WITH THEIR -- THAT'S NOT REALLY A
18 RECOMMENDATION. IT'S REALLY A COMMENT OR AN OPINION.

19 Q AND THE WHO HAS NOT RECOMMENDED THAT PEOPLE
20 REFRAIN FROM DRINKING COFFEE AS A RESULT OF THE CONTENT
21 OF ACRYLAMIDE; CORRECT?

22 A NO, THEY HAVE NOT.

23 Q AND THE WHO HAS RECOMMENDED FURTHER EFFORTS
24 AT DEVELOPING AND IMPLEMENTING MITIGATION MEASURES FOR
25 ACRYLAMIDE IN FOODS OF MAJOR IMPORTANCE FOR DIETARY
26 EXPOSURE, HAVE THEY NOT?

27 A YES.

28 Q AND THE WHO HAS NOT IDENTIFIED COFFEE FOR

1 ANY MITIGATION MEASURE; CORRECT?

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

6 THE COURT: OVERRULED.

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

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

12 A NO.

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

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

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

23 A I DON'T KNOW OF ANY DIFFERENCES.

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

27 MR. METZGER: WELL, OBJECTION; LACKING IN
28 FOUNDATION.

1 THE COURT: OVERRULED.

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

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

7 THE COURT: ALL RIGHT. OBJECTION IS SUSTAINED.

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

13 A NO, I DO NOT.

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

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

19 A CORRECT.

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

22 A I WAS.

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

26 A I DID.

27 Q AND CERT'S PRIMARY ACTIVITY DURING THE
28 PERIOD WHEN YOU SERVED ON THE BOARD OF DIRECTORS WAS

1 ENGAGING IN LITIGATION; CORRECT?

2 A CORRECT.

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

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

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

12 A CORRECT.

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

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

18 Q AND YOU HAVE BEEN RETAINED TO WORK AS AN
19 EXPERT FOR PARTIES REPRESENTED BY MR. METZGER IN ROUGHLY
20 10 TO 15 CASES; IS THAT CORRECT?

21 A CORRECT.

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

23 THE COURT: MAY THE WITNESS BE EXCUSED?

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

26 THE COURT: HOW LONG IS IT GOING TO TAKE?

27 MR. METZGER: THREE MINUTES.

28 THE COURT: OKAY.

REDIRECT EXAMINATION

1
2 BY MR. METZGER:

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

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

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

14 THE COURT: OVERRULED.

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

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

26 BUT IT'S MORE LIKELY THAT IN THE LATE --
27 OTHER TYPES OF CHILDHOOD LEUKEMIA, THAT THE GLYCIDAMIDE-
28 INDUCED MUTATIONS AND THE ACRYLAMIDE DAMAGE TO THE

1 CHROMATIN, NOT THE TOPOISOMERASE II, ARE MORE IMPORTANT.
2 SO THESE THREE MECHANISMS COULD ALL WORK IN
3 CONCERT TO PRODUCE DIFFERENT FORMS OF CHILDHOOD
4 LEUKEMIA.

5 Q BY MR. METZGER: AS FAR AS THE MECHANISM
6 THAT YOU TESTIFIED IS GENERALLY ACCEPTED IN THE
7 SCIENTIFIC COMMUNITY FOR THE DEVELOPMENT OF CHILDHOOD
8 LEUKEMIA, WHICH OF THE THREE THAT YOU'VE JUST MENTIONED
9 IS IT?

10 A IT'S REALLY THE FIRST TWO: THAT CHEMICALS
11 WOULD CROSS AND CAUSE DAMAGE TO THE DNA AND TO THE
12 PROTEINS INTERACTING WITH DNA, LEADING TO CHROMOSOME
13 TRANSLOCATIONS AND STRUCTURAL ABERRATIONS. THE PART
14 ABOUT TOPOISOMERASE II, I AGREE, IS STILL A RESEARCH
15 ISSUE AND IS NOT FULLY ACCEPTED.

16 BUT IT IS ACCEPTED THAT CHROMOSOMAL CHANGES
17 ARISING FROM CHEMICAL EXPOSURES AND RADIATION EXPOSURES
18 IN UTERO ARE IMPORTANT IN THE DEVELOPMENT OF MOST FORMS
19 OF CHILDHOOD LEUKEMIA.

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

22 THE COURT: MAY THE WITNESS BE EXCUSED?

23 MR. SCHURZ: YES, YOUR HONOR.

24 THE COURT: DR. SMITH, YOU MAY STEP DOWN. YOU MAY
25 BE EXCUSED.

26 WHAT'S THE LINEUP FOR THE NEXT WITNESS?

27 MR. METZGER: I APOLOGIZE, YOUR HONOR. THIS WENT
28 MUCH MORE QUICKLY THAN I ANTICIPATED. I DON'T HAVE

1 ANOTHER WITNESS, BUT WE DO HAVE THE PMK TESTIMONY TO
2 ADDRESS, AND WE CAN DO THAT.

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

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

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

10 THE COURT: OKAY.

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

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

14 MR. METZGER: YES.

15 THE COURT: HAS THAT BEEN SUBMITTED ALREADY?

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

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

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

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

24 SO HOW LONG IS THAT WITNESS GOING TO
25 TESTIFY?

26 MR. METZGER: DR. INFANTE WILL BE EXTENSIVE. I'M
27 ANTICIPATING HE'LL CONCLUDE SOMETIME ON WEDNESDAY, AT
28 WHICH POINT WE WILL HAVE DR. HUFF HERE, READY TO GO.

1 THE COURT: AND HOW LONG IS HIS TESTIMONY?

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

5 THE COURT: 10-23. YOU'RE TALKING ABOUT 10-23 AND
6 10-24 FOR HUFF?

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

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

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

13 THE COURT: ALL RIGHT. 10-27 AND 28.

14 AND THEN AFTER PLAINTIFF RESTS, ARE THERE
15 GOING TO BE ANY REBUTTAL WITNESSES?

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

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

20 MR. SCHURZ: SHE'S OUT OF STATE.

21 THE COURT: SO THAT WOULD BE APPROXIMATELY OCTOBER
22 29TH THROUGH OCTOBER 30TH?

23 MR. SCHURZ: I WOULD THINK SO.

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

27 THE COURT: I THINK IT'S VERY GENEROUS, THE TIME
28 FRAME. BUT GO AHEAD.

1 MR. SCHURZ: AND I'M ABSOLUTELY CONFIDENT THAT DR.
2 HUFF ISN'T GOING TO TAKE TWO DAYS. THERE'S --

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

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

9 THE COURT: IS SHE AVAILABLE EARLIER?

10 MR. SCHURZ: I WILL CHECK.

11 THE COURT: ALL RIGHT. WE'LL SEE HOW IT GOES.
12 LET'S SEE IF SHE CAN BE HERE EARLIER RATHER THAN STRETCH
13 IT OUT FOR ANOTHER WEEK.

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

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

20 MR. METZGER: WE DO, YOUR HONOR.

21 THE COURT: ALL RIGHT.

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

24 THE COURT: ALL RIGHT. PLEASE SUBMIT THAT.

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

27 MR. METZGER: WELL, YOUR HONOR --

28 THE COURT: YES.

1 MR. METZGER: -- THERE ARE TWO MATTERS I'D LIKE TO
2 RAISE, IF I MIGHT.

3 THE COURT: OKAY.

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

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

7 MR. METZGER: OKAY.

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

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

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

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

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

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

20 THE COURT: ALL RIGHT.

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

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

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

28 THE COURT: OKAY. ALL RIGHT. SO WE'LL POSTPONE

1 THE DISCUSSION ON THOSE REQUESTS FOR JUDICIAL NOTICE AND
2 OBJECTIONS UNTIL MONDAY, THE 20TH.

3 MR. SCHURZ: THANK YOU, YOUR HONOR.

4 THE COURT: 9:00 O'CLOCK.

5 ALL RIGHT. THANK YOU. HAVE A GOOD WEEK.

6 (AT 11:58 A.M., AN ADJOURNMENT WAS TAKEN
7 UNTIL MONDAY, OCTOBER 20, 2014, AT 9:00 A.M.)
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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

David Eastmond, “Free Radical Mechanisms in Benzene Toxicity,” Ph.D. 1987. Currently Professor of Toxicology at University of California, Riverside.
Martha S. Sandy, “Mechanisms of Paraquat, Diquat and MPTP Cytotoxicity,” Ph.D. 1988. Currently Chief of Toxicology Division at Cal EPA.
Celia G. Evans, “Mechanisms of Resistance to Alkylating Agents in Brain Tumor Cells,” Ph.D. 1988. Currently Senior Toxicologist at Exponent, Seattle, WA.
Moire L. Robertson, “Induction of Micronuclei by Benzene Metabolites: Studies with Isolated Lymphocytes,” Ph.D. 1992. Currently Toxicologist at Variant, Walnut Creek, CA
Kathleen E. Meyer, “Application of Antisense Technology in Determining the Role of Myeloperoxidase in Hydroquinone-Induced Genotoxicity,” Ph.D. 1993. Currently Senior Director, Toxicology at Sangamo BioSciences, San Francisco.
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.

Lee E. Moore, “Use of Fluorescent *in situ* Hybridization (FISH) to Measure Radiation- and Arsenic- Induced Aneuploidy and Micronucleus Formation in Human Exfoliated Cells,” Ph.D. 1994. Currently at the Division of Cancer Epidemiology and Genetics, National Cancer Institute.

Sharan Campleman, “Genotyping of Cytochrome P4502E1 as a Biological Marker of Genetic Susceptibility in Chemical Carcinogenesis: Studies on a Benzene Exposed Cohort,” Ph.D. 1995. Currently scientist at California Breast Cancer Program, Oakland CA.

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.

Elinor Fanning, “New Initiatives in Cancer Risk Assessment: Benzene as a Case Study,” Ph.D. 1998. Associate Director, Research at UCLA-Center for Occupational and Environmental Health

Margy S. Lambert, “Development of a Human Recombinational Mutation Assay and a Mechanistic Model for the Chromosomal Rearrangements in Cancer,” Ph.D. 1999. Lecturer at the University of Wisconsin, Madison.

Laura Gunn, “Biomarkers of Genetic Damage in Children of the Inner city,” M.S. 1999.

Christine Skibola, “Polymorphisms in the Methylenetetrahydrofolate 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..

Laura Gunn, “The Delivery of the FHIT Tumor Suppressor Protein into Lung Cancer Cells,” Ph.D. 2003.

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.

Nygerma Dangleben, “Studies on Effects of Arsenic on Human Beta-Defensin-1.” Ph.D. 2012. Currently a scientist at OEHHA, California EPA.

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.

Gunnilla Ekstrom, 1986-7, now Scientist at AstraZeneca, Sodertalje, Sweden.

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.

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

Joe Shuga, 2007-11, Scientist, Fluidigm, San Francisco.

Recent service as an oral and thesis examiner for doctoral students

Cassandra Calloway, Qualifying Exam, 5/24/2004

Merrill Birkner, Qualifying exam, 5/11/2005. Thesis committee, 2006

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 to Characterize Human Exposure", Invited speaker, National Academy of Sciences meeting on the Exposome, February 24, 2010.

"The Exposome: A Powerful Approach for Evaluating Environmental Exposures and Their Influences on Diseases", Invited speaker, Annual Meeting of the Society of Toxicology, Salt Lake City, UT, March 3, 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.

"Using Omics to Characterize Human Exposure", Invited speaker, International Council of Chemical Associations-Long Range Initiative meeting, Stresa, Italy, June 17, 2010.

"Next Generation Biomarkers and the Exposome", Plenary lecture at UK Environmental Mutagen Society Annual Meeting, Buxton, England, July 12, 2010.

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

“Analyzing the Exposome to find the Environmental Causes of Disease”, Invited plenary lecture, European Union, Brussels, Belgium, September 27, 2010.

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

“Analyzing the Exposome to find the Environmental Causes of Disease”, Invited seminar at University of Utrecht, Institute of Risk Assessment Sciences, The Netherlands, September 29, 2010.

“Benzene: A Prototype Environmental Leukemogen”, EPA NexGen Risk Assessment Meeting, Research Triangle Park, November 2, 2010.

2011

“Benzene: A Prototype Environmental Leukemogen”, EPA NexGen Risk Assessment Meeting, Washington DC, February 15, 2011.

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

“Methodologies for analyzing the exposome – The Exposome Alliance”, Lecture at Annual Environomarkers Meeting, Athens, Greece, March 7, 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

“Finding the causes of hematological cancers” ILSI-HESI Award Lecture, Society of Toxicology, San Francisco, CA, March 12, 2012.

“Measuring cell death and genotoxicity in single cells and human populations using lab-on-a-chip technologies”, Invited Symposium speaker, Society of Toxicology, San Francisco, CA, March 12, 2012.

“Using omics in the risk assessment of benzene”, Invited speaker at International Congress on Occupational Health, Cancun, Mexico, March 21, 2012.

“The Early Life Exposome and Future Disease Risk,” Prenatal Programming and Toxicity International Conference (PPTOX III) meeting, Paris France, May 14-16, 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.

“Transcriptomics,” Invited speaker at International Agency for Research on Cancer, Lyon, France, October 17, 2012.

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

“The Exposome Paradigm,” Keynote Opening Lecture at AACR Special Conference on Post-GWAS Horizons in Molecular Epidemiology: Digging Deeper into the Environment, Hollywood, FL, November 11-14, 2012.

2013

“The Exposome and Early Life Exposures”, Invited speaker at symposium on Childrens Environmental Health at CalEPA in Sacramento, CA, Jan 16, 2013.

“The Exposome Paradigm”, Invited seminar to Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, February 12, 2013.

“Genome-Exposome Interactions in Leukemia Etiology”, Invited keynote speaker, conference organizer and session co-chair at meeting on "The Bone Marrow Niche, Stem Cells and Leukemia: Impact of Drugs, Chemicals, and the Environment," New York Academy of Sciences, New York, May 29-31, 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

“An Exposome approach to finding the causes of leukemia”, Invited keynote speaker at Annual meeting of the UK Environmental Mutagen Society, Bristol, UK, July 15, 2013.

“Introduction to the Exposome”, Opening lecture at Superfund Research Program meeting, Berkeley, CA, September 20, 2013.

“The Exposome: Where do we go from here”, Invited speaker and session co-chair, Annual meeting of the Environmental Mutagen and Genomics Society, Monterey CA, September 23, 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.

“The Exposome Paradigm,” Invited Plenary speaker at meeting of the Chinese Society of Toxicology, Guangzhou, China, November 13, 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- present)
Cell Biochemistry and Function (2008-present)

Prior member of Editorial Board of:

Environmental Health Perspectives (2003 – 2008)
Free Radical Research (1990 –2000)
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.

Head of Genomics and New Technologies Special Interest Group for the Environmental Mutagen Society, 2003-7.

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

1. **Smith MT**, Darmon J, Wills ED, Dondi PG (1979) Rapid data analysis in quantitative cytochemistry. *Histochem J.* 11:370-371. PMID 457443.
2. **Smith MT**, Loveridge N, Wills ED, Chayen J (1979) The distribution of glutathione in the rat liver lobule. *Biochem J.* 182:103-108. PMID 496899.
3. **Smith MT**, Wills ED, Drew K, Maxwell C, Daly JR, Reader SCJ, Robertson WR (1980) The use of an inexpensive, general purpose microcomputer in quantitative cytochemistry. *Histochem J.* 68:321-323. PMID 7462006.
4. **Smith MT**, Wills ED (1981) Effects of dietary lipid and phenobarbitone on the distribution and concentration of cytochrome P-450 in the liver studied by quantitative cytochemistry. *FEBS Letters.* 127:33-36. PMID 7250371.
5. **Smith MT**, Wills ED (1981) Effect of dietary lipid and phenobarbitone on the production and utilization of NADPH in the liver. A combined biochemical and quantitative cytochemical study. *Biochem J.* 200:691-699. PMID 7342977.
6. Henderson B, Loveridge N, Robertson WR, **Smith MT** (1981) The influence of the storage of tissue blocks at -70°C on enzyme activity: a quantitative cytochemical study. *Histochemistry.* 72:545-550. PMID 7298388.
7. **Smith MT**, Thor H, Orrenius S (1981) Toxic injury to isolated hepatocytes is not dependent on extracellular calcium. *Science.* 213: 1257-1259. PMID 7268433.
8. **Smith MT**, Thor H, Hartzell P, Orrenius S (1982) The measurement of lipid peroxidation in isolated hepatocytes. *Biochem Pharmacol.* 31:19-26. PMID 7059346.
9. Jewell SA, Bellomo G, Thor H, Orrenius S, **Smith MT** (1982) Bleb formation in hepatocytes during drug metabolism is caused by disturbances in thiol and calcium ion homeostasis. *Science.* 217:1257-1259. PMID 7112127.
10. Thor H, **Smith MT**, Hartzell P, Bellomo G, Jewell SA, Orrenius S (1982) The metabolism of menadione in isolated hepatocytes. A study of the implications of oxidative stress in intact cells. *J Biol Chem.* 257:12419-12425. PMID 6181068.
11. **Smith MT**, Thor H, Orrenius S (1983) Role of lipid peroxidation in the toxicity of foreign compounds to liver cells. *Biochem Pharmacol.* 32:763-764. PMID 6838624.

12. Jones DP, Thor H, **Smith MT**, Jewell SA, Orrenius S (1983) Inhibition of ATP-dependent microsomal Ca²⁺ sequestration during oxidative stress and its prevention by glutathione. *J Biol Chem.* 258:6390-6393. PMID 6406479.
13. Cohen GM, Wilson GD, Gibby EM, **Smith MT**, Doherty MD, Connors T (1983) 1-Naphthol: A potential anti-cancer agent. *Biochem Pharmacol.* 32:2363-2365. PMID 6882476.
14. **Smith MT**, Redick JA, Baron J (1983) Quantitative immunocytochemistry: A comparison of microdensitometric measurement of unlabeled antibody peroxidase-antiperoxidase staining and of microfluorometric measurement of indirect fluorescent antibody staining for NADPH-cytochrome (P-450) reductase. *J Histochem Cytochem.* 31:1183-1189. PMID 6411804.
15. de Peyster A, Quintanilha A, Packer L, **Smith MT** (1984) Oxygen radical formation induced by gossypol in rat liver microsomes and human sperm. *Biochem Biophys Res Commun.* 118:573-579. PMID 6322752.
16. Doherty MD, Cohen GM, **Smith MT** (1984) Mechanisms of toxic injury to isolated hepatocytes by 1-naphthol. *Biochem Pharmacol.* 33:543-549. PMID 6200119.
17. Thornalley PJ, Doherty MD, **Smith MT**, Bannister JM, Cohen GM (1984) The formation of active oxygen species following activation of 1-naphthol, 1,2- and 1,4-naphthoquinone by rat liver microsomes. *Chem-Biol Interact.* 48:195-206. PMID 6321045.
18. Chesis PL, Levin DB, **Smith MT**, Ernster L, Ames BN (1984) Mutagenicity of quinones: pathways of metabolic activation and detoxification. *Proc Natl Acad Sci USA.* 81:1696-1700. PMID 6584903.
19. **Smith MT** and Evans CG. (1984) Inhibitory effect of superoxide generating quinones on superoxide dismutase. *Biochem Pharmacol.* 33:3109-3110. PMID 6091670.
20. Fluck DS, Rappaport SM, Eastmond DA, **Smith MT** (1984) Conversion of 1-naphthol to naphthoquinone metabolites by rat liver microsomes: Demonstration by high pressure liquid chromatography with electrochemical detection. *Arch Biochem Biophys.* 235:351-358. PMID 6517596.
21. **Smith MT**, Fluck DS, Eastmond DA, Rappaport SM (1985) Detection of quinone metabolites by HPLC with reductive electrochemical detection. *Life Chemistry Reports.* 3:250-258. PMID 6517596.
22. Talcott RE, **Smith MT**, Giannini DD (1985) Inhibition of microsomal lipid peroxidation by naphthoquinones: Structure-activity relationships and possible mechanisms of action. *Arch Biochem Biophys.* 241:88-94. PMID 4026326.
23. **Smith MT**, Thompson S (1985) Free radical and alcoholics. *Lancet.* 2:774-775. PMID 2864501.
24. **Smith MT**, Sandy MS (1985) Role of extracellular Ca²⁺ in toxic liver injury: comparative studies with the perfused liver and isolated hepatocytes. *Toxicol Appl Pharmacol.* 81:213-219. PMID 4060150.
25. Thompson S, **Smith MT** (1985) Measurement of a diene conjugated form of linoleic acid in plasma by hplc: A questionable non-invasive assay of free radical activity. *Chem-Biol Interact.* 55:357-367. PMID 4075442.
26. Ross D, Mehlhorn R, Moldeus PW, **Smith MT** (1985) Metabolism of diethylstilbesterol by horseradish peroxidase and prostaglandin synthase: generation of a free radical intermediate and its interaction with glutathione. *J Biol Chem.* 260:16210 - 16214. PMID 2999150.
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