Appendix D

Index of Public Comments Submitted before the Peer Review Meeting

United States
Environmental Protection Agency
Office of Research and Development

Peer Review Workshop on EPA's Draft External Review Document "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization"

Holiday Inn Capitol Plaza
Sacramento, CA
March 5–6, 2002

List of Pre-workshop Public Comments

(Received as of 3/6/02)

Acculabs, Inc.
The Analysis of Perchlorate in Groundwater and Soil by Electrospray LC/MS/MS

Alliance for Responsible Water Policy
Written Oral Comments

American Council on Science and Health (ACSH)
Written Oral Comments

American Water Works Association (AWWA)
Letter

American Water Works Service Company, Inc.
Letter

The Boeing Company and The Perchlorate Study Group
Assessment of the Potential Human Health Risk Caused by Exposure to Perchlorate

CF Industries, Inc. (CF)
Letter

Consultants in Epidemiology and Environmental Health
- Letter
- Analysis of T4/TSH vs. Iodine in NHANES III Data
- Benchmark Doses for Perchlorate Obtained from Lamm et al. (1999) Study of Thyroid Function in Perchlorate Workers
- Cancer of the Thyroid Perchlorate
- Comments on Brechner et al. (JOEM, 2000)
- E-mail from Steve Lamm (data)
- Exploration of the Jackie Schwartz Dissertation
- Fetal and Neonatal Human Hormone Changes
- Goitrogens in the Environment
- Human Exposure to Environmental Perchlorate and Iodine – A Public Health Perspective
- Lack of relationship between neonatal T4 and neurobehavioral disorders
- Neurobehavioral Diseases in Nevada Counties with Respect to Perchlorate in Drinking Water
- Neonatal Thryoxine Level and Perchlorate in Drinking Water
- Newborn Thyroxine Levels and Childhood ADHD

- Occupational and Environmental Health Aspects of Perchlorate
- Perchlorate and Human Health: Literature Summary
- Perchlorate Clinical Pharmacology and Human Health: A Review
- Perchlorate – Overview of Human Data
- Review: Therapeutic Drug Monitoring in Pediatrics
- Similar Effects of Thionamide Drugs and Perchlorate on Thyroid-Stimulating Immunoglobulins in Graves' Disease: Evidence Against an Immunospressive Action of Thionamide Drugs
- Thyroid Health Status of Ammonium Perchlorate Workers: A Cross-Sectional Occupational Health Study

Crump, Casey
Addendum to submission by Kerr-McGee Corporation

Department of Defense Perchlorate Working Group
Comments on the U.S. Environmental Protection Agency's Draft Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization (NCEA-1-0503, 16 January 2002)

Department of Defense - Office of the Under Secretary of Defense
Letter

Department of Health Services (State of California, Health and Human Services Agency)
Letter

Environmental Working Group
Letter

Fisher, Jeffrey, University of Georgia
Letter

Goodman, Gay
Thyroid Function, Perchlorate Mode of Action, and Interspecies Differences: Comments on the EPA/NCEA External Review Draft of January 16, 2002

Greer, Monte
Why it is essential to use human dose-response data to evaluate the human health hazard from perchlorate concentrations in drinking water

Greer, Monte; Goodman, Gay; Pleus, Richard; Greer, Susan
Health Effects Assessment for Environmental Perchlorate Contamination: The Dose- Response for Inhibition of Thyroidal Radioiodine Uptake in Humans

Intertox
- Assessment of Neuropsychlogical Studies by Haddow et al. (1999) and Others Cited by U.S. EPA to Support Their Concerns for Developmental Deficits Related to Maternal Thyroid Deficiency – Executive Summary
- Assessment of Neuropsychlogical Studies by Haddow et al. (1999) and Others Cited by U.S. EPA to Support Their Concerns for Developmental Deficits Related to Maternal Thyroid Deficiency
- Assessment of the Validity of U.S. EPA's Interpretation of an Effect of Altered Neurobehavior in Offspring Treated with Perchlorate *in Utero*: A Critical Review of the Argus (1998) and Bekkedal et al. (2000) Studies – Executive Summary
- Assessment of the Validity of U.S. EPA's Interpretation of an Effect of Altered Neurobehavior in Offspring Treated with Perchlorate *in Utero*: A Critical Review of the Argus (1998) and Bekkedal et al. (2000) Studies

- Review and Assessment of TSH and Thhyroid Hormones during Pregnancy in the Rat and Human and Comparison to Hormone Values in the 2001 Effects Study – Executive Summary
- Review and Assessment of TSH and Thyroid Hormones during Pregnancy in the Rat and Human and Comparison to Hormone Values in the 2001 Effects Study
- Summary of the Expert Review of the Argus, 2001 ("Effects Study") Evaluation of Perchlorate Effects on Brain Morphometry in Neonatal Rats – Executive Summary
- Summary of the Expert Review of the Argus, 2001 ("Effects Study") Evaluation of Perchlorate Effects on Brain Morphometry in Neonatal Rats
- Summary of the 1999 External Peer Review Panel Workshop – Executive Summary
- Summary of the 1999 External Peer Review Panel Workshop

Kerr-McGee Corporation
Assessment of the Potential Human Health Risk Caused by Exposure to Perchlorate

Koren, Gideon
Letter

Ladd, Larry
Letter

Lockheed Martin Corporation
Comments on: Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization (External Review Draft January 16, 2002)

Lockheed Martin Corporation
Comments on EPA's Draft "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization"

Los Alamos National Laboratory
Letter

McNabb, Anne
Letter

Parsons Engineering
- Letter
- Technical Memorandum

The Rooney Group
Written Oral Comments

Schwartz, Harold
Thyroid Hormone Effects on the Developing Brain: Critical Review of Data Presented in a Neurodevelopmental Study in Rats by Argus Laboratories (the 2001 "Effects Study") with Reference to an Earlier Neurodevelopmental Study by Argus Laboratories (the 1998 Developmental Neurotoxicity Study) and a Subchronic Study by Springborn Laboratories (the 90-Day Testing Strategy Bioassay in Rats): Comments on the EPA/NCEA External Review Draft of January 16, 2002

Schwartz, Jackie
Gestational exposure to perchlorate is associated with measures of decreased thyroid function in a population of California neonates.

Toxicology Excellence for Risk Assessment
- Quantitative Evaluation of Perchlorate Risk Assessment
- Use of Human Data in Perchlorate Risk Assessment

Texas Natural Resource Conservation Commission (TNRCC)
Letter

The Fertilizer Institute (TFI)
Letter

Vinson & Elkins L.L.P.
Letter

Wahlsten, Douglas
- Perchlorate effects on neonatal rat brain morphometry: A critical evaluation
- Perchlorate effects on rat motor activity: A critical evaluation
- Summary and Re-Analysis of Data: Brain Morphometry Results from a Perchlorate Toxicity Study (Primedica 2001)

White, La Donna
Written oral comments

Appendix E

Index of Public Comments Submitted after the Peer Review Meeting

United States
Environmental Protection Agency
Office of Research and Development

Peer Review Workshop on EPA's Draft External Review Document "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization"

Holiday Inn Capitol Plaza
Sacramento, CA
March 5–6, 2002

List of Post-workshop Public Comments

(Comments received between 3/7/02 and 4/5/02)

Aerospace Corporation
Assessment of Perchlorate Releases in Launch Operations

Alliance for Responsible Water Policy
Letter

American Water Works Association
Letter

Association of California Water Agencies
Letter

California Public Interest Research Group
Letter

California Cancer Registry, Region 5
- Community Cancer Assessment in Redlands California, 1988-1998
- Community Cancer Assessment in Response to Long-time Exposure to Perchlorate and Trichloroethylene in Drinking Water (Abstract)

Cocopah Indian Tribe
Letter

Consultants in Epidemiology and Occupation Health, Inc.
- Letter
- Comments on Brechner et al. (JOEM, 2000) [Note: Previously submitted, submitted here as a reference to above letter]
- Perchlorate Effects on the Thyroid – Clinical Laboratory Confirmation of Occupational Epidemiology Findings [Submitted here as a reference to above letter]
- Benchmark Doses for Perchlorate Obtained from Lamm et al. (1999) Study of Thyroid Function in Perchlorate Workers [Note: Submitted here as a reference to above letter]

Department of Defense
Consultative letter

Environmental Working Group
EPA's Proposed Perchlorate RfD: Not Good Enough

Goodman, Gay
Graphical Analysis Reveals Anomalies in the Thyroid Hormone Results of the Developmental Toxicity Studies in Rats Performed in Support of the EPA Risk Assessment for Perchlorate: Comments on the EPA/NCEA External Review Draft of January 16, 2002

Intertox
Letter

Kerr-McGee Corporation
Assessment of the Potential Human Health Risk Caused by Exposure to Perchlorate – Supplemental comments submitted to the Environmental Protection Agency and The External Peer Review Panel

Leighton, Patrick
Letter

Los Alamos National Laboratory and Los Alamos County
Los Alamos National Laboratory and Los Alamos County Comments on Perchlorate Rulemaking

Lockheed Martin Corporation
Comments on U.S. EPA's Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization

Metropolitan Water District of Southern California
Letter

Parsons Engineering Science, Inc.
Letter

Perchlorate Study Group
Letter
CD

Note: Many of the documents on the CD were perviously submitted. New or revised documents that are not listed above include:

- Chronic Environmental Exposure to Perchlorate and Thyroid Function During Pregnancy and the Neonatal Period (Tellez et al.)
- Does Perchlorate in Drinking Water Affect Thyroid Function in Newborns or School Age Children (Crump et al.)
- Evaluation of a Population with Occupational Exposure to Airborne Ammonium Perchlorate for Possible Acute or Chronic Effects on Thyroid Function (Gibbs et al.)
- Letter to Goehl (Goodman)
- Written oral comments (Guth)
- Letter (Intertox)
- Public Health Goal for Perchlorate in Drinking Water (Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)
- Thyroid Function, Perchlorate Mode of Action, and Interspecies Differences: Comments on the EPA/NCEA External Review Draft of January 16, 2002 (Goodman) [REVISED]

Pingaro, Daniel
Letter

Southern Nevada Water Authority
Letter

State of Nevada, Department of Environmental Protection
Letter

Wahlsten, Douglas
Perchlorate effects on brain morphometry

List of Public Comments Submitted After Deadline

(Comments received after 4/5/02)

Note: Comments were submitted to EPA, but were not forwarded to the peer reviewers

Consultants in Epidemiology and Occupation Health, Inc.

- E-mail [Subject: Perchlorate and the Mammary Gland]
- Effect of prolactin on sodium iodine symporter expression in mouse mammary gland explants
- Enhanced iodine concentrating capacity by the mammary gland in iodine deficient lactating women of an endemic goiter region in Sicily
- E-mail [Subject: Response to Comments on Lawrence Studies]
- Letter-to-the editor (received by Thyroid Journal)
- Response to Bruckner-Davis *et al.*

SQM North America
Letter

Appendix F

List of Registered Observers of the Peer Review Meeting

United States
Environmental Protection Agency
Office of Research and Development

Peer Review Workshop on EPA's Draft External Review Document "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization"

Holiday Inn Capitol Plaza
Sacramento, CA
March 5–6, 2002

Final List of Observers

George Alexeeff
Director of Scientific Affairs
Office of Environmental
Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street - 16th Floor
Oakland, CA 94612
510-622-3202
Fax: 510-622-3210
E-mail: galexeef@oehha.ca.gov

Doris Anders
Toxicologist
U.S. Air Force
HQ Air Force Center for Environmental
Excellence / ERC
3207 North Road
Brooks Air Force Base, TX 78235-5344
210-536-5667
Fax: 210-536-5989
E-mail: doris.anders@brooks.af.mil

Richard Barfield
Assistant Counsel for Environmental Law
Southern Division
Office of Counsel
Naval Facilities Engineering Command
P.O. Box 180010
North Charleston, SC 29419-9010
843-820-5661
E-mail: BarfieldRA@efdsouth.navfac.navy.mil

Ambika Bathija
Office of Water
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW (4304T)
Washington, DC 20460
202-566-1087
E-mail: bathija.ambika@epa.gov

Jeanne Bauer
Neighborhood Eyes
2260 Ramo Court
Rancho Cordova, CA 95670
916-638-2077

Barbara Beck
Principal, Risk Assessment
Gradient Corporation
238 Main Street
Cambridge, MA 02142
617-395-5000
Fax: 617-395-5001
E-mail: bbeck@gradientcorp.com

Marni Bekkedal
Deputy Director
Neurobehavioral Effects Laboratory
Naval Health Research
Center Toxicology Detachment
Building 433 - 20612 5th Street
Wright-Patterson Air Force Base, OH 45433
937-255-6058
Fax: 937-656-7094
E-mail: marni.bekkedal@wpafb.af.mil

Charles Berrey
Superfund Division
U.S. Environmental Protection Agency
75 Hawthorne Street (SFD 7-2)
San Francisco, CA 94105
415-972-3146
E-mail: berrey.charles@epa.gov

David Berry
Senior Toxicologist
HERD
DTSC
P.O. Box 806
Sacramento, CA 95812-0806
916-255-6626
Fax: 916-255-6657
E-mail: dberry@dtsc.ca.gov

Joel Bird
President
Acculabs, Inc.
4663 Table Mountain Road
Golden, CO 80215
303-277-9514
Fax: 303-277-9512
E-mail: labvpbird@yahoo.com

Kelly Bitner
Environmental Geologist
Neptune and Company
4600A Montgomery Boulevard, NW - Suite 100
Albuquerque, NM 87109
505-884-8455
Fax: 505-884-8475
E-mail: bitner@neptuneandco.com

Thomas Blackman
Senior Hydrogeologist
Camp Dresser & McKee, Inc.
21300 Victory Boulevard - Suite 840
Woodland Hills, CA 91367
213-219-3555
Fax: 818-702-1789
E-mail: blackmantd@cdm.com

Anita Bonifacio
Region 9
U.S. Environmental Protection Agency
75 Hawthorne Street (SFD-3)
San Francisco, CA 94105
415-972-3231
E-mail: bonifacio.anita@epa.gov

Steven Book
Drinking Water Program
California Department of Health Services
601 North 7th Street
P.O. Box 942732 (MS 92)
Sacramento, CA 94234-7320
916-322-1553
Fax: 916-323-1382
E-mail: sbook@dhs.ca.gov

Jonathan Borak
Associate Clinical Professor of
Medicine and Epidemiology
School of Medicine
Yale University
234 Church Street #1100
New Haven, CT 06520
203-777-6611
Fax: 203-777-1411
E-mail: jborak@att.net

Richard Canady
Toxicologist
U.S. Food and Drug Administration
5100 Paint Brush Parkway
College Park, MD 20740-3835
301-436-1944
Fax: 301-436-2632
E-mail: rcanady@cfsan.fda.gov

Maria de la Paz Carpio-Obeso
Environmental Specialist
Colorado River Basin Region
California Water Quality Control Board
73-720 Fred Waring Drive - Suite 100
Palm Desert, CA 92260
760-674-0803
E-mail: carpm@rb7.swrcb.ca.gov

Kathleen Carroll
Water/Wastewater Treatment Supervisor
Utility Administration
Public Works Department
City of Yuma
155 West 14th Street
Yuma, AZ 85364
928-343-8814
Fax: 928-343-8852
E-mail: kathleen.carroll@ci.yuma.az.us

Robin Casale
American Water Works Service Company
880 Kuhn Road
Chula Vista, CA 91914
619-656-2422
E-mail: rcasale@amwater.com

Traci Case
AWWA Research Foundation
6666 West Quincy Avenue
Denver, CO 80235
303-347-6120
Fax: 303-730-0851
E-mail: tcase@awwarf.com

Harlal Choudhury
Director
Superfund Health Risk Technical Support Center
National Center for Environmental Assessment (MS-117)
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268
513-569-7536
Fax: 513-569-7475
E-mail: choudhury.harlal@epa.gov

Jaimie Clark
Toxicologist
Komex
11040 Santa Monica Boulevard
Suite 300
Los Angeles, CA 90025
310-914-5901
Fax: 310-914-5959
E-mail: jclark@losangeles.komex.com

Krista Clark
Regulatory Affairs Specialist
Association of California Water Agencies
910 K Street - Suite 100
Sacramento, CA 95814-3512
916-441-4545
Fax: 916-325-2306
E-mail: kristac@acwanet.com

Rebecca Clewell
Research Scientist
Geo-Centers, Inc.
HEST
Air Force Research Laboratory
2856 G. Street - Building 79
Wright-Patterson Air Force Base, OH 45433
937-255-5150
Fax: 937-255-1474
E-mail: rebecca.clewell@wpafb.af.mil

Ann Codrington
Associate Branch Chief
Targeting and Analysis Branch
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue (4607M)
Washington, DC 20460
202-564-4688
E-mail: codrington.ann@epa.gov

Patrick Corbett
Director Environmental Affairs
Remediation and Planning
Kerr-McGee Chemical LLC
Kerr-McGee Center
P.O. Box 25861
Oklahoma City, OK 73125
405-270-3774
Fax: 405-270-3058
E-mail: pcorbett@kmg.com

Mark Craig
Environmental Engineer
Southern Division
Naval Facilities Engineering Command
Department of Navy
2155 Eagle Drive
North Charleston, SC 29419
843-820-5517
Fax: 843-820-5563
E-mail: craigm@efdsouth.navfac.navy.mil

Kevin Crofton
Toxicologist
Neurobehavioral Toxicology Branch
Neurotoxicology Division
U.S. Environmental Protection Agency (MD-74B)
Research Triangle Park, NC 27711
919-541-2672
Fax: 919-541-4849
E-mail: crofton.kevin@epa.gov

Jerald Cross
Environmental Scientist
Region 8
U.S. Environmental Protection Agency
999 18th Street - Suite 300 (8EPR-F)
Denver, CO 80202-2466
303-312-6664
Fax: 303-312-6067
E-mail: cross.jerald@epa.gov

Larry Cummings
Director, Safety & Environmental Engineering
American Pacific
P.O. Box 629
Cedar City, UT 84721
435-865-5018
Fax: 435-865-5005
E-mail: lcummings@apfc.com

Jane Diamond
Director
Superfund Division
U.S. Environmental Protection Agency
75 Hawthorne Street (SFD-1)
San Francisco, CA 94105
415-972-3275
E-mail: diamond.jane@epa.gov

Joan Dollarhide
Toxicologist
Toxicology Excellence for Risk Assessment
1757 Chase Avenue
Cincinnati, OH 45223
502-857-2707
Fax: 502-857-2706
E-mail: dollarhide@tera.org

Michael Dourson
Director
Toxicology Excellence for Risk Assessment
1757 Chase Avenue
Cincinnati, OH 45223
513-542-7474
Fax: 513-542-7487
E-mail: dourson@tera.org

David Dunson
Biostatistics Branch
National Institute of
Environmental Health Sciences (MD A3 – 03)
Research Triangle Park, NC 27709
919-541-3003
Fax: 919-541-4311
E-mail: dunson1@niehs.nih.gov

Stephen Ellington
Environmental Safety Engineer
Air Force Contract
Detachment 9/Vannenberg AFB
SRS Technologies
150 North "N" Street
Lompoc, CA 93436
805-606-3071
Fax: 805-606-2058
E-mail: stephen.ellington@vanvenberg.af.mil

Anna Fan
Chief, Pesticide and Environmental Toxicology
Office of Environmental
Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street - 16th Floor
Oakland, CA 94612
510-622-3165
Fax: 510-622-3218
E-mail: afan@oehha.ca.gov

Lisa Fasano
Press Officer
Region 9
U.S. Environmental Protection Agency
75 Hawthorne Street (OPA-1)
San Francisco, CA 94105
415-947-4307
E-mail: fasano.lisa@epa.gov

Linda Ferguson
Director, Safety & Environmental Engineer
American Pacific
3770 Howard Hughes Parkway - Suite 300
Las Vegas, NV 89109
702-699-4133
Fax: 702-794-0714
E-mail: lferguson@apfc.com

Malcolm Garg
Consultant Support for the
Army Environmental Programs
CH2M Hill/U.S. Army
600 Army Pentagon (DAIM-ED-M)
Washington, DC 20310
703-693-0678
Fax: 703-697-0338
E-mail: malcom.garg@hqda.army.mil

Richard Garrett
Municipal Services Director
City of Waco
P.O. Box 2570
Waco, TX 76702
254-750-8040
Fax: 254-750-8032
E-mail: pollyf@ci.waco.tx.us

David Garrison
Regional Environmental Manager
Regional Environmental Office
Center for Environmental Excellence
U.S. Air Force
505 South Griffin - Suite 505
Dallas, TX 75202
214-767-4652
Fax: 214-767-4661
E-mail: mike.garrison@dallafcee.brooks.af.mil

John Gaston
Executive Director
Alliance for Responsible Water Policy
1115 11th Street
Sacramento, CA 95814
510-251-2888
Fax: 510-893-8205
E-mail: jgaston@ch2m.com

Jeffrey Gebhart
Water Operations Manager
City of Henderson, Nevada
240 Water Street
Henderson, NV 89015
702-565-0616
Fax: 702-565-4272
E-mail: jlg@ci.henderson.nv.us

Andrew Geller
Research Psychologist
Neurophysiological Toxicology Branch
Neurotoxicology Division
NHEERL
U.S. Environmental Protection Agency (MD-74B)
Research Triangle Park, NC 27711
919-541-4208
E-mail: geller.andrew@epa.gov

Bill George
Senior Counsel
KPC Communications
1115 Eleventh Street - Suite 230
Sacramento, CA 95814
916-444-2671
Fax: 916-444-0159
E-mail: Bgeorge@ka-pow.com

Herman Gibb
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW (8601D)
Washington, DC 20460
202-564-3334
Fax: 202-565-0059
E-mail: gibb.herman@epa.gov

John Gibbs
Kerr-McGee
P.O. Box 25861
Oklahoma City, OK 73125
405-270-2909
Fax: 405-270-3526
E-mail: jgibbs@kmg.com

John Gibson
CEO
American Pacific Corporation
3770 Howard Hughes Parkway – Suite 300
Las Vegas, NV 89109
702-699-4140
Fax: 702-794-0714
E-mail: jogibson@apfc.com

Michael Girard
Chairman, Perchlorate Study Group
Aerojet
Building 2001 Department 0330
P.O. Box 13222
Sacramento, CA 95813-6000
916-355-2945
Fax: 916-355-6145
E-mail: michael.girard@aerojet.com

Jonathan Gledhill
Consultant
The EOP Group, Inc.
819 Seventh Street, NW
Washington, DC 20001
202-833-8940
Fax: 202-833-8945

Larry Glidewell
Public Affairs
U.S. Department of Defense
Building 262 - Room N-152
4375 Chidlaw Road
Wright-Patterson Air Force Base, OH 45433
937-257-6946
Fax: 937-257-2558
E-mail: larry.glidewell@wpafb.af.mil

Stefan Gogosh
Senior Engineer
Water/Wastewater Group
Environmental Planning/Water Resources
Engineering Division
URS Corporation
2020 East 1st Street - Suite 400
Santa Ana, CA 92705
714-433-7644
Fax: 714-433-7701
E-mail: stefan_gogosha@urscorp.com

Gay Goodman
Chief Toxicologist
Human Health Risk Resources, Inc.
1711 29th Avenue West
Seattle, WA 98199
206-284-4820
Fax: 206-284-8425
E-mail: ggDABT@earthlink.net

Monte Greer
Professor of Medicine
Oregon Health & Science University
3181 Southwest Sam Jackson Park Road
Portland, OR 97201
503-494-8484
Fax: 503-494-6990
E-mail: greerm@ohsu.edu

Charles Griffice
Senior Project Engineer
The Aerospace Corporation
P.O. Box 92957 (M5/564)
Los Angeles, CA 90009-2957
310-336-1121
Fax: 310-336-0230
E-mail: charles.p.griffice@aero.org

Michael Griffith
Research Ecologist
National Center for Environmental Assessment
U.S. Environmental Protection Agency
26 West Martin Luther King Drive (MS 190)
Cincinnati, OH 45268
513-569-7034
Fax: 513-569-7475
E-mail: griffith.michael@epa.gov

Bill Guarini
Vice President, Government Programs
Envirogen
4100 Quakeridge Road
Lawrenceville, NJ 08648
609-936-9300
Fax: 609-936-9221
E-mail: guarini@envirogen.com

Dan Guth
Toxicologist
Boeing Company
P.O. Box 3707 (7A-WK)
Seattle, WA 98124-2207
425-865-6935
Fax: 425-865-6619
E-mail: daniel.j.guth@boeing.com

William Hall
Director, Product Stewardship
IMC Global Operations
3095 County Road - 640 West
Mulberry, FL 33860
863-428-7161
Fax: 863-428-7398
E-mail: wlhall@imcglobal.com

Ed Hansen
District Manager
Magna Water Company
2711 South 8600 West
P.O. Box 303
Magna, UT 84044
801-250-2118
Fax: 801-250-1452
E-mail: hansene@magnawater.com

Brian Harre
Engineer
U.S. Navy
Naval Facilities Engineering Service Center
1100 23rd Avenue - Code 411
Port Hueneme, CA 93043-4370
805-982-1795
Fax: 805-982-4304
E-mail: harrebl@nfesc.navy.mil

Barbara Hartman
Administrative Assistant
Superfund Division
Region 9
U.S. Environmental Protection Agency
75 Hawthorne Street (SFD-1)
San Francisco, CA 94501
415-947-8709
Fax: 415-947-3528
E-mail: Hartman.Barbara@epa.gov

Kyle Headley
Environmental Planner
Brazos River Authority
P.O. Box 7555
Waco, TX 76714
254-761-3167
Fax: 254-761-3204
E-mail: kheadley@brazos.org

Allan Hirsch
Deputy Director, External and Legislative Affairs
External Affairs Unit
Office of Environmental
Health Hazard Assessment
California Environmental Protection Agency
1001 I Street
P.O. Box 4010
Sacramento, CA 95812
916-324-0955
Fax: 916-323-8803
E-mail: ahirsch@oehha.ca.gov

Susanna Hitchcock
Water Quality Assurance Supervisor
Pretreatment Division
Public Works Department
City of Yuma
155 West 14th Street
Yuma, AZ 85364
928-343-8814
Fax: 928-343-8852
E-mail: susanna.hitchcock@ci.yuma.az.us

Michael Honeycutt
Toxicologist
Texas Natural Resource Conservation Commission
P.O. Box 13087 (168)
Austin, TX 78711
512-239-1793
Fax: 512-239-1794
E-mail: mhoneycu@tnrcc.state.tx.us

Robert Howd
Senior Toxicologist
Office of Environmental
Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street - 16th Floor
Oakland, CA 94612
510-622-3168
Fax: 510-622-3218
E-mail: bhowd@oehha.ca.gov

David Huber
Regulation Manager
Office of Ground and Drinking Water
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue (4607M)
Washington, DC 20004
202-564-4878
Fax: 202-564-3760
E-mail: huber.david@epa.gov

Tupper Hull
Senior Counsel
KPC Communications
1115 Eleventh Street - Suite 230
Sacramento, CA 95814
916-444-2671
Fax: 916-444-0159
E-mail: thull@ka-pow.com

Janis Hulla
Senior Toxicologist
Environmental Engineering
U.S. Army Corps of Engineers
1325 J Street
Sacramento, CA 95814
916-557-7561
Fax: 916-557-5307
E-mail: janishulla@aol.com

Sujatha Jahagirdar
Drinking Water Associate
CALPIRG
3435 Wilshire Boulevard - Suite 385
Los Angeles, CA 90010
213-251-3680
Fax: 213-251-3699
E-mail: sujatha@calpirg.org

Annie Jarabek
Special Assistant to the
Associate Director for Health
National Center for Environmental Assessment - Immediate Office
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC
919-541-4847
Fax: 919-541-1818
E-mail: jarabek.annie@epa.gov

Susan Jew
Director, Environmental Services
Thiokol Propulsion
Alliant Tech Systems
P.O. Box 707
Brigham City, UT 84302
435-863-2287
Fax: 435-863-3151
E-mail: susan.jew@thiokol.com

Mark Jones
Toxicologist
MWH
777 Campus Commons - Suite 175
Sacramento, CA 95825
916-565-4205
Fax: 916-569-3258
E-mail: mark.k.jones@mwhglobal.com

Todd Kantorczyk
Attorney at Law
Gibson, Dunn & Crutcher LLP
1050 Connecticut Avenue, NW - Suite 900
Washington, DC 20036
202-887-3608
Fax: 202-467-0539
E-mail: tkantorczyk@gibsondunn.com

William Kelly
Western Representative
Center for Regulatory Effectiveness
184 Mt. Owen Drive
Driggs, ID 83422
208-354-3050
Fax: 208-354-3050
E-mail: wgkelly@tetontel.com

Laura Kennedy
Kennedy/Jenks Consultants
622 Folsom Street
San Francisco, CA 94107
415-243-2405
Fax: 415-896-0999
E-mail: LauraKennedy@KennedyJenks.com

Gary Kimmel
Developmental Toxicologist
National Center for Environmental Assessment
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW (8623 D)
Washington, DC 20460
202-564-3308
Fax: 202-565-0078
E-mail: kimmel.gary@epa.gov

Velma Knight
Civil Engineer
Tulsa District
U.S. Army Corps of Engineers
1645 South 101st East Avenue
Tulsa, OK 74128
918-669-7047
Fax: 918-669-7508
E-mail: dawn.knight@usace.army.mil

Dan Kowalczyk
Booz Allen Hamilton
8283 Greensboro Drive
Hamilton Room #4088
McLean, VA 22102-3838
703-902-4176
Fax: 703-902-3559
E-mail: kowalczyk_daniel@bah.com

Theodore Krawczyk
Environmental Program Manager
SMC/AZFV
U.S. Air Force
2420 Vela Way - Suite 1467
El Segundo, CA 90245
310-363-2419
Fax: 310-363-1503
E-mail: theodore.krawczyk@losangeles.af.mil

Larry Ladd
Interim Chair
Community Advisory Group
Aerojet Superfund Group
11064 Santiam River Court
Rancho Cordova, CA 95670-2820
916-852-8188
E-mail: llladd@sprintmail.com

Steven Lamm
Chief Scientist
Consultants in Epidemiology
and Occupational Health
2428 Wisconsin Avenue, NW
Washington, DC 20007
202-333-2364
Fax: 202-333-2239
E-mail: steve@ceoh.com

Valerie Lang
System Engineering Director
The Aerospace Corporation
P.O. Box 92957 (M5/564)
Los Angeles, CA 90009-2957
310-336-1170
Fax: 310-336-0230
E-mail: valerie.I.lang@aero.org

J. David Lawson
Oklahoma Department of Environmental Quality
707 North Robinson
P.O. Box 1677
Oklahoma City, OK 73101-1677
405-702-5104
Fax: 405-702-5101
E-mail: david.lawson@deq.state.ok.us

Tom Lewandowski
Risk Assessment Division
Gradient Corporation
9725 SE 36th Street - Suite 404
Mercer Island, WA 98040
206-275-4767
Fax: 206-275-4775
E-mail: tlewando@gradientcorp.com

George Linkletter
Principal
Environ
2010 Main Street - Suite 900
Irvine, CA 92614
848-261-5131
Fax: 949-261-6202
E-mail: glinkletter@environcorp.com

John Locke
Environmental Engineer
Environmental Department
U.S. Navy
33000 Nixie Way
Building 50 - Suite 326 (N45125)
San Diego, CA 92147-5110
619-524-6405
Fax: 619-524-6519
E-mail: locke.john.b@asw.cnrsw.navy.mil

Cornell Long
Chief, Health Risk Assessment Branch
Air Force Institute for Environment, Safety and
Occupational Health Risk Analysis
U.S. Air Force
2513 Kennedy Circle
Brooks Air Force Base, TX 78235-5116
210-536-6121
Fax: 210-536-1130
E-mail: cornell.long@brooks.af.mil

Alex MacDonald
Regional Water Quality Control Board
California Environmental Protection Agency
3443 Routier Road - Suite A
Sacramento, CA 95827-3003
916-255-3025
Fax: 916-255-3052
E-mail: MacDonA@rb5s.swrcb.ca.gov

Bruce Macler
Drinking Water Toxicologist
Region 9
U.S. Environmental Protection Agency
75 Hawthorne Street (WTR6)
San Francisco, CA 94105
415-972-3569
Fax: 415-947-3549
E-mail: macler.bruce@epa.gov

Robert MacPhail
Chief
Neurobehavioral Toxicology Branch
Neurotoxicology Division
U.S. Environmental Protection Agency (MD-74B)
Research Triangle Park, NC 27711
919-541-7833
E-mail: macphail.robert@epa.gov

Mick Major
Program Manager
Center for Health Promotion
and Preventative Medicine
U.S. Army
5158 Blackhawk Road (MCHB-TS-THE)
Abredeen Proving Ground, MD 21010
410-436-7159
Fax: 410-436-8258
E-mail: michael.major@apg.amedd.army.mil

Mary Manibusan
Human Health Toxicologist
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW (MC 4607M)
Washington, DC 20460
202-564-5265
Fax: 202-564-3760
E-mail: manibusan.mary@epa.gov

Allan Marcus
Statistician
Environmental Media Assessment Group
National Center for Environmental Assessment
U.S. Environmental Protection Agency (MD-52)
Research Triangle Park, NC 27711
919-541-0636
Fax: 919-541-1818
E-mail: marcus.allan@epa.gov

Jon Marshak
Staff Environmental Scientist
Center Valley Regional Water
Quality Control Board
3443 Routier Road - Suite A
Sacramento, CA 95827
916-255-3123
Fax: 916-255-3015
E-mail: marshaj@rb5s.swrcb.ca.gov

Ken Martins
Industrial Water Specialist
CH2M Hill
3 Hutton Centre Drive - Suite 200
Santa Ana, CA 92707
714-429-2020
Fax: 714-424-2094
E-mail: kmartins@ch2m.com

David Mattie
Senior Research Toxicologist/Director of
Research Operations
HEST
Air Force Research Laboratory
2856 G Street - Building 79
Wright - Patterson Air Force Base, OH 45433
937-255-3423
Fax: 937-255-1474
E-mail: david.mattie@wpafb.af.mil

Kevin Mayer
Region 9
U.S. Environmental Protection Agency
75 Hawthorne Street (SFD-7-2)
San Francisco, CA 94195-3901
415-972-3176
Fax: 415-947-3526
E-mail: mayer.kevin@epa.gov

Catherine McCracken
Mediator and Facilitator
480 Warren Drive, #204
San Francisco, CA 94131
415-596-8409
Fax: 415-759-8831
E-mail: cmccrackensf@aol.com

Mike Meadows
Environmental Section Manager
Brazos River Authority
P.O. Box 7555
Waco, TX 76714-7555
254-761-3150
Fax: 254-761-3201
E-mail: mikem@brazos.org

Markus Meier
Eberhardt Meier Cassel
700 Petal Court - Suite A
Vacaville, CA 95688-9289
707-330-1757
Fax: 707-474-2552
E-mail: mmeier@emcenviron.com

Elaine Merrill
Operational Technologies
HEST
Air Force Research Laboratories
2856 G Street - Building 79
Wright - Patterson Air Force Base, OH 45433
937-255-5150
Fax: 937-255-1474
E-mail: elaine.merrill@wpafb.af.mil

Mark Miller
Public Health Medical Officer
California Environmental Protection Agency
1515 Clay Street - 16th Floor
Oakland, CA 94612
510-622-3159
Fax: 510-622-3210
E-mail: mmiller@oehha.ca.gov

Amy Mills
Environmental Scientist
Integrated Risk Information Systems
National Center for
Environmental Risk Assessment
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue (8601D)
Washington, DC 20460
202-564-3204
Fax: 202-565-0075
E-mail: amy.mills@epa.gov

Kathi Moore
Region 9
U.S. Environmental Protection Agency
75 Hawthorne Street (SFD-2)
San Francisco, CA 94105
415-972-3144
E-mail: moore.kathi@epa.gov

Mary Morningstar
Lockheed Martin
5324 McKinley Street
Bethesda, MD 20814
301-897-6685
Fax: 301-897-6998
E-mail: mary.p.morningstar@lmco.com

Hyland Morrow
Project Manager
Sacramento District
U.S. Army Corps of Engineers
1325 J Street
Sacramento, CA 95814
916-557-6924
Fax: 916-557-7865
E-mail: hyland.b.morrow@usace.army.mil

William Nelson
Senior Regional Representative
Region 9
Agency for Toxic Substances
& Disease Registry
75 Hawthorne Street - Suite 100, MS: HHS-1
San Francisco, CA 94105
415-947-4316
Fax: 415-947-4323
E-mail: WQN1@cdc.gov

Penny Newman
Executive Director
Center for Community Action
and Environmental Justice
P.O. Box 33124
Riverside, CA 92519
909-360-8451
Fax: 909-360-5950
E-mail: newmanp@pe.net

Eric Newman
Esquire
Kahl/Pownall Companies
1115 11th Street
Sacramento, CA 95814
916-448-2162
Fax: 916-448-4923
E-mail: enewman@ka-pow.com

Alicia Paatsch
Chemist
Gannett Flemming
1411 Fourth Avenue - Suite 850
Seattle, WA 98101
206-467-6072
Fax: 206-467-1167
E-mail: apaatsch@gfnet.com

Randy Palachek
Parsons Engineering Science Inc.
8000 Centre Park Drive - Suite 200
Austin, TX 78754
512-719-6006
Fax: 512-719-6099
E-mail: randy.m.palachek@parsons.com

Zahra Panahi
Principal Engineer
Water Division
Public Utilities Department
City of Riverside
3900 Main Street
Riverside, CA 92522
909-826-5612
Fax: 909-826-2498
E-mail: ZPANAHI@ci.riverside.ca.us

Brent Payne
Senior Project Manager
Water/Wastewater Group
Environmental Planning/Water Resources
Engineering Division
URS Corporation
2020 East 1st Street - Suite 400
Santa Ana, CA 92705
714-433-7650
Fax: 714-433-7701
E-mail: brent_payne@urscorp.com

Curtis Payton
Technical Team Lead
Environmental Geology
Engineering Division
U.S. Army Corps of Engineers
1325 J Street (SPK-ED-EG)
Sacramento, CA 95814
916-557-7431
Fax: 916-557-7865
E-mail: curtis.payton@usace.army.mil

Richard Pleus
Principal
Intertox, Inc.
2819 Elliott Avenue - Suite 201
Seattle, WA 98121-1122
206-443-2115
Fax: 206-443-2117
E-mail: rcpleus@intertox.com

Brenda Pohlmann
Bureau Chief
Las Vegas Operations
Nevada Division of Environmental Protection
555 East Washington Avenue - Suite 4300
Las Vegas, NV 89101-1049
702-486-2857
E-mail: bpohlman@govmail.state.nv.us

Jonna Polk
Project Manager
Tulsa District
U.S. Army Corps of Engineers
1645 South 101st East Avenue
Tulsa, OK 74128
918-669-7482
Fax: 918-669-7206
E-mail: jonna.polk@usace.army.mil

Offie Porat Soldin
Soldin Research and Consultants, Inc.
6308 Walhonding Road
Bethesda, MD 20816
301-320-3535
Fax: 301-229-5285
E-mail: offie@gwu.edu

Ronald Porter
Lead Biologist
Center for Science and Technology
Mitretek Systems
13526 George Road - Suite 200
San Antonio, TX 78244
210-479-0478
Fax: 210-479-0482
E-mail: ronald.porter@mitretek.org

Bill Pratt
Manager, Environmental & Facilities Engineering
United Technologies
600 Metcalf Road - Building 12
San Jose, CA 95138
408-776-4951
Fax: 408-776-4820
E-mail: billp@csd.com

Jason Preece
Camp Dresser & McKee Inc.
100 Pringle Avenue - Suite 300
Walnut Creek, CA 94596
925-296-8055
E-mail: PreeceJE@cdm.com

Roman Racca
Public Participation Specialist
California Department of
Toxic Substance Control
8800 California Center Drive
Sacramento, CA 95826
916-255-6684
Fax: 916-255-3654
E-mail: RRacca@dtsc.ca.gov

Steve Rembish
Parsons Engineering Science, Inc.
8000 Centre Park Drive - Suite 200
Austin, TX 78754
512-719-6067
Fax: 512-719-6099
E-mail: steve.j.rembish@parsons.com

David Rexing
SNWS Water Quality R&D Project Manager
SNWS Water Quality
Southern Nevada Water System
342 Lakeshore Road
Boulder City, NV 89005
702-567-2035
Fax: 702-567-2085
E-mail: d.rexing@lvvwd.com

Catherine Roberts
Community Development Coodinator
U.S. Environmental Protection Agency
999 18th Street - Suite 300 (80C)
Denver, CO 80202
303-312-6025
Fax: 303-312-6961
E-mail: roberts.catherine@epa.gov

Dan Rodgers
Lieutenant Colonel
U.S. Air Force
Department of Defense
1250 Thomas Avenue - Suite 222
Little Rock, AR 72099
501-987-8162
Fax: 501-987-6854
E-mail: drogers@jag.af.mil

Raimund Roehl
Research Scientist
Sanitation and Radiation Laboratory
California Department of Health Services
2151 Berkeley Way
Berkeley, CA 94704
510-540-2204
Fax: 510-540-2053
E-mail: Rroehl@dhs.ca.gov

Peter Rooney
Principal
Rooney Group
P.O. Box 19223
Sacramento, CA 95819
916-374-9749
Fax: 916-375-6543
E-mail: rooney@rgroup.net

David Rose
Major
Restoration Attorney
Air Force Legal Services Agency, Environmental
Law and Litigation Division
U.S. Air Force
1501 Wilson Boulevard - Suite 629
Arlington, VA 22209
703-369-6901
Fax: 703-696-9184
E-mail: david.rose@pentagon.af.mil

David Rosenfeld
Journalist
Natural Resources News Service
210 South Helberta Avenue
Redondo Beach, CA 92077
310-318-3009
Fax: 310-379-1937
E-mail: rosenfeld@publicedcenter.org

Gilbert Ross
American Council on Science and Health
1995 Broadway - 2nd Floor
New York, NY 10023
212-362-7044
Fax: 212-362-4919
E-mail: ross@acsh.org

Jackie Schwartz
Environmental Health Investigations Branch
California Department of Health Services
1515 Clay Street - Suite 1700
Oakland, CA 94612
510-622-4487
Fax: 510-622-4505
E-mail: Jschwartz@dhs.ca.gov

Renee Sharp
Environmental Working Group
1904 Franklin Street - Suite 515
Oakland, CA 94612
510-444-0974
Fax: 510-444-0982
E-mail: renee@ewg.org

Val Siebal
Chief Deputy Director
Office of Environmental
Health Hazard Assessment
California Environmental Protection Agency
1001 I Street - P.O. Box 4010
Sacramento, CA 95812-4010
916-324-2831
Fax: 916-327-1097
E-mail: vsiebal@oehha.ca.gov

Ralph Smialowicz
National Health Effects and
Environmental Risk Laboratory
Experimental Toxicology Division
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711
919-541-5776
Fax: 919-541-3538
E-mail: smialowicz.ralph@epa.gov

Philip Smith
Assistant Research Professor
The Institute of Environmental
and Human Health
Texas Tech University
P.O. Box 41163
Lubbock, TX 79409
806-885-4567
Fax: 806-885-2132
E-mail: phil.smith@tiehh.ttu.edu

Jennifer Stiltz
Associate Environmental Engineer
Sacramento Division
Foster Wheeler Environmental
1047 Lennae Drive - Suite 200
Sacramento, CA 95833
916-928-4854
E-mail: jstiltz@fwenc.com

Shane Synder
SNWS Water Quality R&D Project Manager
SNWS Water Quality
Southern Nevada Water System
342 Lakeshore Road
Boulder City, NV 89005
702-567-2317
Fax: 702-567-2085
E-mail: shane.snyder@lvvwd.com

David Ting
Toxicologist
Office of Environmental
Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street - 16th Floor
Oakland, CA 94612
510-622-3226
Fax: 510-622-3218
E-mail: dting@oehha.ca.gov

Marcia Torobin
Metropolitan Water District of Southern California
P.O. Box 54153
Los Angeles, CA 90054-0153
213-217-7830
Fax: 213-217-6951
E-mail: mtorobin@mwdh2o.com

Glenn Totten
BNA - Environmental Reporter
P.O. Box 1775
Orangevale, CA 95662
916-965-6723
Fax: 916-962-1868
E-mail: gtotten@ix.netcom.com

Marilyn Underwood
Staff Toxicologist
Environmental Health Investigations Branch
California Department of Health Services
1515 Clay Street - Suite 1700
Oakland, CA 94612
510-622-4415
Fax: 510-622-4505
E-mail: munderwo@dhs.ca.gov

Kurt Urquhart
Director, Environmental, Health & Safety
Seating & Propulsion Systems
Goodrich Corporation
P.O. Box KK
3530 Bransconme Road
Fairfield, CA 94533
707-399-1899
Fax: 707-422-1818
E-mail: kurquhart@oeaa.com

David Vecera
Attorney
Air Force Materiel Command/JAV
U.S. Air Force
4225 Logistic Avenue - Suite 23
Wright-Patterson Air Force Base, OH 45433
937-656-0210
Fax: 937-257-0537
E-mail: dave.vecera@wpafb.af.mil

Steve Via
American Water Works Association
1401 New York Avenue, NW - Suite 640
Washington, DC 20005
202-628-8303
E-mail: svia@awwa.org

Rudy vonBerg
Toxicologist
IT Corporation
4005 Port Chicago Highway
Concord, CA 94520
925-288-2366
Fax: 925-287-2148
E-mail: rvonberg@theitgroup.com

George Waegell
Neighborhood Eyes
2260 Ramo Court
Rancho Cordova, CA 95670
916-638-2077

Douglas Wahlsten
Department of Psychology
University of Alberta
BioSci P461
Edmonton, AB T6G 2E9 CANADA
780-492-2549
Fax: 780-492-1768
E-mail: wahlsten@ualberta.ca

Bill Wallner
Environmental Scientist
Division of Solid and Hazardous Waste
Department of Environmental Quality
State of Utah
P.O. Box 144880
Salt Lake City, UT 84114-4880
801-538-6742
Fax: 801-538-6715
E-mail: bwallner@deq.state.ut.us

LaDonna White
Faculty Physician with Methodist Hospital
Capitol Medical Society
7500 Hospital Drive
Sacramento, CA 95823
916-681-1618
Fax: 916-688-0225
E-mail: L2White@chw.edu

Casey Whittier
Product Manager
U.S. Filter
1901 South Prairie Avenue
Waukesha, WI 53189
262-521-8506
Fax: 262-547-4120
E-mail: whittierc@usfilter.com

Sharon Wilbur
Environmental Health Scientist
Division of Toxicology
Agency for Toxic Substances
and Disease Registry
1600 Clifton Road, NE (MS E29)
Atlanta, GA 30333
404-498-0704
Fax: 404-498-0092
E-mail: sdw9@cdc.gov

Wenona Wilson
Coordinator
Region 9
U.S. Environmental Protection Agency
75 Hawthorne Street (SFD - 3)
San Francisco, CA 94105
415-972-3239
Fax: 415-947-3528
E-mail: wilson.wenona@epa.gov

Paul Winkler
Director of Special Analytical Service
Acculabs, Inc.
4663 Table Mountain Road
Golden, CO 80215
303-277-9514
Fax: 303-277-9512
E-mail: labvpbird@yahoo.com

Jody Wireman
Environmental Toxicologist
Air Force Institute for Environment, Safety and
Occupational Health Risk Analysis
U.S. Air Force
2513 Kennedy Circle
Brooks Air Force Base, TX 78235-5116
210-536-6123
Fax: 210-536-1130
E-mail: jody.wireman@brooks.af.mil

Karen Wirth
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue (MC 4607M)
Washington, DC 20460
202-564-5846
Fax: 202-564-3760
E-mail: wirth.karen@epa.gov

Douglas Wolf
National Health Effects and
Environmental Risk Laboratory
Experimental Toxicology Division
U.S. Environmental Protection Agency
86 T.W. Alexander Drive
Research Triangle Park, NC 27711
919-541-4137
Fax: 919-541-0694
E-mail: wolf.doug@epa.gov

Allen Wolfenden
Department of Toxics Substances Control
P.O. Box 806 (CC1-SF)
Sacramento, CA 95812-0806
916-255-6540
E-mail: awolfend@dtsc.ca.gov

Stan Zawistowski
Site Assessment Manager
Federal Facilities Branch
Region 8
U.S. Environmental Protection Agency
999 18th Street - Suite 500 (8EPR-F)
Denver, CO 80202
303-312-6255
Fax: 303-312-6067
E-mail: zawistowski.stan@epa.gov

Kim Zikmund
Project Manager
Southern Nevada Water Authority
1900 East Flamingo - Suite 255
Las Vegas, NV 89130
702-822-3380
Fax: 702-822-3396
E-mail: kim.zikmund@lvvwd.com

Doug Zimmerman
Bureau Chief, Bureau of Corrective Actions
Nevada Division of Environmental Protection
333 West Nye Lane
Carson City, NV 89701
775-687-4670
Fax: 775-687-6396
E-mail: dzimmerm@govmail.state.nv.us

Appendix G

Agenda for the Peer Review Meeting

Peer Review Workshop on EPA's Draft External Review Document "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization"

Holiday Inn Capitol Plaza
Sacramento, CA
March 5–6, 2002

Agenda

Workshop Chair: **Ronald Wyzga, Electric Power Research Institute**
Facilitator: **Jan Connery, Eastern Research Group, Inc.**

T U E S D A Y , M A R C H 5 , 2 0 0 2

8:00 AM **Registration/Check-In**

8:30 AM **Welcome and Announcements**
Jan Connery

8:35 AM **Opening Remarks**
Herman Gibb, Acting Associate Director for Health, U.S. EPA, ORD/NCEA, Washington, DC
Jane Diamond, Superfund Deputy Director, U.S. EPA, Region 9

8:50 AM **Reviewer Introductions/Conflict-of-Interest Disclosure**
Jan Connery

9:10 AM **Background on EPA's Revised Draft, "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization"**
Annie Jarabek, U.S. EPA, ORD/NCEA, Research Triangle Park, NC

9:30 AM **Charge to the Reviewers**
Ronald Wyzga

9:45 AM B R E A K

10:00 AM **Topic Area A: Hazard Characterization and Mode of Action**
Discussion leader: Thomas Zoeller

11:00 AM **Topic Area B: Human Health Effects Data**
Discussion leader: David Hoel

12:00 Noon L U N C H

12:30 PM **Observer Comment Period**

T U E S D A Y , M A R C H 5 , 2 0 0 2 ***(c o n t i n u e d)***

1:30 PM **Topic Area C: Laboratory Animal Studies**
Discussion leaders: Michael Collins, Developmental Toxicity; Thomas Collins, ReproductiveToxicity; Thomas Zoeller, Endocrine and Neuroendocrine; Gary Williams, Pathology; *Michael Aschner, Neurotoxicity; Loren Koller, Immunotoxicity*

3:30 PM B R E A K

3:45 PM **Topic Area D: Ecological Risk Assessment and Evidence for Indirect Exposure**
Discussion leader: William Adams

5:15 PM **Closing Remarks**
Ron Wyzga and Jan Connery

5:30 PM A D J O U R N

W E D N E S D A Y , M A R C H 6 , 2 0 0 2

8:00 AM **Observer Comment Period**

8:30 AM **Review of Day One Discussions and Charge to Reviewers**
Ron Wyzga

8:45 AM **Topic Area E: Use of PBPK Modeling**
Discussion leader: Michael Kohn

9:45 AM B R E A K

10:00 AM **Topic Area E: Use of PBPK Modeling** (continued)
Discussion leader: Michael Kohn

11:00 AM **Topic Area F: Human Health Dose-Response Assessment**
Discussion leader: Thomas Collins

12:30 PM L U N C H

1:30 PM **Topic Area G: Risk Characterization**
Discussion leader: Ron Wyzga

3:00 PM B R E A K

3:15 PM **Topic Area H: General Questions, Conclusions, and Recommendations**
Discussion leader: Ron Wyzga

4:15 PM **Closing Remarks**

4:30 PM A D J O U R N

Appendix H

Public Comments Provided Orally during the Peer Review Meeting

Note: The peer review meeting included three designated observer comment periods. This section includes verbatim transcripts of the observer comments, in the order the comments were given.

Larry Glidwell, U.S. Department of Defense (DoD)

Good afternoon everybody. I hope everybody had a great lunch. More detailed discussions of the following, as well as any additional DoD comments on the Agency's risk assessment methodology and conclusions, is provided in the comments submitted by the Department of Defense perchlorate docket. In the area of human health and toxicology, although the Department of Defense contributed data used by EPA in the risk assessment, DoD does not support all the conclusions as stated in the document, nor does DoD support EPA's proposed revised RfD value. However, we do believe the harmonized assessment based perchlorate's inhibition of iodine uptake as the mode of action represents the major EPA chemical risk characterization. In addition, we believe that the careful evaluation and use of availability dosimetry modeling, all to perform cross-species dosimetry in lieu of defaults, as well as to evaluate the potential for age-dependent sensitivity differences, is a strong point of the EPA risk characterization.

In regards with risk assessment characterization, the use of analysis of epidemiological studies, EPA's perchlorate risk characterization puts too much weight on the results of certain animal studies. This data selectively creates a biased, or fatally flawed, perchlorate risk characterization. While human studies data, including the epidemiological, occupational, and clinical information, were presented and discussed in Chapter 4, given the perception that the data were factored into EPA's decision, the data and the studies were not used to derive the draft perchlorate RfD.

In addition, it is apparent that the Agency has provided an unbalanced consideration of available epidemiological studies. The Agency dismissed several well-conducted, published studies that were negative, while giving great credence to one unpublished graduate study that was positive. The fact that the two studies have demonstrated that workers exposed to very high concentrations of perchlorate do not display alterations of thyroid function is an important piece of information for evaluating the risk for perchlorate exposure. In the graduate study, the odds ratios for perchlorate exposure as a presumptive positive for congenital hypothyroidism were in the opposite direction compared to increase in exposure. Therefore, the odds ratios for the high exposure group were likely due to chance. Thank you.

Marni Bekkedal, Naval Health Research Center Toxicology Defense

Implementation of a weight-of-the-evidence approach for the selection of the point of departure is potentially more subjective than the traditional approach of separate calculations on each candidate critical study or endpoint. The Agency selected a point of departure in the rat of 0.01 mg/kg/day. The basis is provided by multiple analyses over many studies and endpoints. Analyses include conventional significance testing, benchmark analysis, Bayesian statistical analysis, ANOVA, and profile analysis. These endpoints reflect exposures ranging from a few weeks to a large fraction of a lifetime, from gestation to adulthood. The validity of characterizing all these results with a single point of departure must be questioned.

There's no evidence to support immunotoxicity as a more sensitive critical effect than the developmental endpoints used as the basis for this assessment. The difficulty of implementing EPA's weight-of-the-evidence approach is illustrated by the Agency's rationale for calling the 0.01 mg/kg/day point of departure a LOAEL based on four class of endpoints: (1) profile analysis of brain morphometry effects in neonatal rats; (2) increased motor activity in neonatal rats; (3) thyroid histopathology; and (4) thyroid hormone changes in a number of studies. Only two of these—brain morphometry and hormone analyses—actually demonstrated effects at the cited point of departure. Both of these classes of endpoints are highly inconsistent, suggesting a problem identifying this dose as a LOAEL or NOAEL.

EPA's policy on changes in brain morphometry is that, in the absence of data that would prove otherwise, changes in the size of a particular brain region are considered adverse. However, in the absence of a consistent dose-response or data that would support the assertion that the observed responses could be the result of compensatory mechanisms, there is no conclusive evidence that demonstrates changes in brain region size were exposure related. Given the uncertainty associated with the small sample size, considering these changes a LOAEL may not be justified. The ability of humans to more easily maintain blood thyroid hormone levels is important with regard to the developmental toxicity of perchlorate, where decreases in thyroid hormone in fetal and neonatal rats are believed to influence brain development and perhaps induce changes in brain morphometry.

The other basis for describing the point of departure as the LOAEL is the results of hormonal analysis in several studies indicating changes in T4, T3, and TSH at doses as low as 0.01 mg/kg/day. However, these changes are not consistent and, as with the brain morphometry data, should be considered an equivocal LOAEL/NOAEL, justifying an uncertainty factor of at most 3. Chemicals which inhibit thyroid hormone synthesis would not result in the dramatic changes in blood T4/T3 levels in humans that have been reported in the rat. Doses that result in alterations in blood thyroid hormone levels in rats, and consequently produce the developmental effects observed in the brain of rats, would not be expected to produce similar disruption in humans, due to the presence of TBG, which is also present in the developing human fetus and neonate.

Mike Dourson, Toxicology Excellence for Risk Assessment

Mike Dourson, Toxicology Excellence for Risk Assessment. We are a non-profit group in Cincinnati, Ohio, with a mission to protect public health. We're funded on this activity by the Perchlorate Study Group, but the comments we're going to make are those of our own, and not theirs. We appreciate EPA's accommodation of public comments and really all their hard work. We applaud the partnership of federal, state, industry, consulting, academic, and non-profit scientists that helped make this evaluation possible.

TERA scientists generated the first two perchlorate reference doses and had one of them externally peer reviewed. It was appropriately critiqued, principally due to the lack of data. Our

role since that time has been to monitor toxicity studies and to share information with public and private groups, when requested. The key findings that we have here is that decreased serum T4 should be designated as the critical effect because it's a known precursor to other adverse effects in the thyroid and brain. Pregnant animals or women are a sensitive sub-population. EPA's weight-of-evidence analysis and support of a point of departure should be rethought, because it ignores data that does not support its position and fails to evaluate the adverse nature of each of the endpoints discussed. Furthermore, we agree with several reviewers that human data should be used as a reality check. We would focus on the critical effect of decreased T4.

Moreover, we feel that the quality of the human database is sufficient for deriving a human-based reference dose. Dramatic, dynamic differences between the rat and humans in their responses following iodide uptake inhibition suggests that using the animal data as the basis of the RfD will introduce an unnecessary degree of uncertainty and excess conservatism in the assessment. For example, EPA's RfD is approximately 230-fold lower than the threshold for inhibition of iodide uptake found in the Greer et al. 2001 study.

We feel the most appropriate point of departure for a perchlorate reference dose is a benchmark dose analysis on the data from Greer et al. 2002. The study followed the common rule. A benchmark dose lower limit of 0.02 mg/kg/day, based on the 20% inhibition of iodide uptake, was identified by us as an appropriate point of departure since no effect was observed on serum T4 levels in Greer 2002 and other chronic human exposures. In fact, doses up to 70% inhibition appear to be without hormone changes.

So, in conclusion, we again thank EPA for accommodating our comments. We recommend that the perchlorate reference dose be based on human data. This RfD has more confidence than that based on rats and is possibly more protective of human health.

John Gibbs, Kerr-McGee Chemical LLC

For over 10 years, I've been responsible for medical surveillance at Kerr-McGee's Nevada facilities, where perchlorate was produced. In 1997, there were no studies of health effects from chronic low-level exposure to perchlorate in humans. We used the then newly available analytical technique to measure levels in air, studied employees in our Nevada facilities, and found no thyroidal or other health effects related to chronic or single-shift exposures up to 30 mg/day.

In 1998, Dr. Lamm studied the only other U.S. workforce with significant exposure to perchlorate. He measured perchlorate in urine and calculated absorbed doses across work shifts, which correlated well with doses estimated from simultaneous airborne exposures, confirming the rapid systemic absorption to the respiratory route. Dr. Kenny Crump analyzed the Lamm data set and determined that the BMDL was 44–58 mg/day for hormonal effects in healthy working adults.

We found perchlorate present naturally in groundwater in northern Chile, where nitrate fertilizer was applied; located three coastal cities with water supplies where well-defined, containing non-detectable, 6, and 110 parts per billion perchlorate. We studied approximately 50 first graders with lifelong residence in each city and obtained neonatal TSH data from these same cities for a 3-year period. We found no decrease in T4 or increase in TSH associated with perchlorate in water supplies. Frozen urine and serum samples are currently being analyzed by the Air Force Research Laboratory. We expect to have those values very soon.

Until very recently, we were unaware of the shifting concern regarding the most sensitive subpopulation, from infants and children to the first trimester fetus. We are convinced that northern Chile is the best laboratory in which to evaluate this concern. Accordingly, a study of pregnant women in the same three cities has been commissioned. We expect to follow approximately 50 pregnancies from the first trimester through delivery in each city and have the study completed in 2003.

Upon reviewing some of the early literature on perchlorate, such as Stanbury and Wyngaarden, it is apparent that perchlorate is not unique in its ability to block iodide uptake by the thyroid. Several other inorganic anions share the same pharmacology, only with differing potencies. Two of those—thiocyanate and nitrate—are present in many of the foods we consider healthy, such as broccoli, lettuce, spinach, cabbage, and milk. The relative impact of NIS inhibition from normal dietary sources overshadows the possible contribution from perchlorate in drinking water in most areas where perchlorate is detectable. Furthermore, in the past few years, [inaudible] has been demonstrated that there is dramatic synergism between soy in rodent diet and iodine deficiency. By inference, a soy diet will be synergistic with perchlorate in causing thyroid hormone effects. In the influential rodent studies referenced in the draft assessment, the rats were fed diets consisting of approximately 25% soy. This unrecognized confounder renders the “Effects Study” inappropriate as a departure point for risk assessment at this time.

I’ve included full-text copies of the specific studies to which I’ve just referred in written comments. I encourage members of the panel to read them. Thank you.

Richard Pleus, Intertox, Inc.

Thank you very much for the opportunity to speak with you. I’m here to more or less to give a reality check on the neurodevelopmental studies. I’m going to be talking a little bit about, and my papers are about, the behavior from both an animal and human standpoint. I have basically three questions and I’ve outlined them in green here to help point them to you. In addition, if you look on the top side of this, you’ll see the papers we have presented to you and they are identified by reference here so you will have an opportunity to go back to those papers and take a loot at them. So, hopefully that will make it a little bit easier. In addition, I’ve got a couple of things in lighter green to help you orient to some of the questions that may also be brought up.

The three questions I have are, were the perchlorate doses high enough to cause any adverse health effects in laboratory animals. I think that's a very fundamental question and I would request that you take a look at the study that we wrote. Also, you might look at the study by Dr. Goodman and also a study by Dr. Wahlsten. Why is that important? Well, if you don't have a high enough perchlorate dose, you're not going to get any effects.

Were the studies conducted correctly? On two of those aspects, both the behavior and also the morphometry, the question is, I think, valid. On the morphometry, we had five experts take a look at the way that the process was done for brain morphometry and their conclusions are both summarized here on the front page as well as in the documents. Was the behavior analyzed correctly? And I think if you take a look at the documents that were provided in the CD by the authors, you'll find that when they did statistical analysis using repeated measures ANOVA, in fact, there were no significant effects. Also, I want to point you to the fact that we have set up a Web site. For those that are not neuro-anatomically inclined, if you want to take a look at what we have—an animation that might help you understand a little bit more about the process. Please take a look, it's there. The logon is "rat" and the password is "brain."

Lastly, did the EPA document correctly assess the literature, both from an animal and a human standpoint? I think there are some interesting questions here. Number one, for example, in the literature, it is very clear that, from a behavioral aspect, auditory startle habituation is a documented sensitive indicator of neurodevelopmental effects by reduction of hypothyroidism. So I would encourage you to take a look at that, what is listed in the literature versus what was actually reported in the risk assessment. And then lastly on the [inaudible] studies, Haddow and a bunch of other documents have been cited, and I would say take a look at the document that we wrote on that, which we say effectively information was selectively taken. Thank you.

Gay Goodman, Human Health Risk Resources, Inc.

The first tabled item is actually Monte's presentation. The second one was supposed to be my presentation, but then I was asked to talk about something else. I was asked to talk about the iodine in the human study, and so I tacked on that page 7 that you see, which really doesn't belong with the presentation but I had to stick it somewhere so that's what the last page is. So first I'm going to talk about the iodine. Then, if I have time, I'll go back to my actual presentation, which is related to the interpretation of the animal data.

Basically I wanted to say whoever earlier, it was said that, it was a weakness of the human study; I was the co-investigator on the study. Dr. Monte Greer, who is the next speaker, was the principal investigator. A weakness of that study is that the dietary iodine was not controlled in these people. And yes, that's a difficulty; it makes very difficult to tease out the influence of iodine on the inhibition for two reasons. One is because we didn't control it. And second is, even though we measured iodine throughout the study, on exposure day 1 and 2, certainly the highest dose and possibly the next highest dose, there was an iodine excretion was increased in these people. And so it's very difficult to look at the relationship. However, I'm very much

involved in analyzing these data, and I've done a lot already, and you can expect within a couple of weeks to receive a manuscript that describes the relationship of the [inaudible] uptake on the iodine, as best as we can analyze it in these subjects. So basically what I'm saying is expect a thorough analysis of the subject. To give you a heads up, there is a dependence and it doesn't depend on the percent; if you analyze it in terms of percent inhibition of uptake, it doesn't work. In other words, you have to factor in something that accounts for low iodine versus high iodine. You can't just look at percent inhibition of uptake and expect that to apply over the whole range of iodine. So there is a nuance to these data and you can look for the data.

Now I have 1 minute to talk my regular presentation. Basically I wanted to say that I do not believe that the mode of action proposed by EPA applies very well to these animal data, if at all, because these animals were extremely over-sufficient in iodine and they were able to escape from the inhibition by up-regulating in a manner that does not go through the pattern that is described in the EPA document. What happens in over iodine sufficiency, and there is plenty of data, if you look at the data, and I don't have time to describe it, but there are plenty of data showing that after the initial acute phase, these animals had up-regulated and were no longer inhibited after a couple of days. So, certainly in the 14-day studies, 90-day studies, developmental studies, there was no inhibition of iodide uptake, by any criteria. Period. End of story. There is no inhibition of iodide uptake, then there must be some mechanism for why T3 and T4 were down, TSH was up.

I have plenty more to say on this. Some of it's in there. Look for another two presentations from me, written presentations, one on the human, one on the animal.

Monte Greer, Oregon Health and Science University

Good afternoon. Can you hear me OK? I'm Monte Greer. My name has been mentioned a couple of times today. I thought you'd like to see what I look like, but those of you in the back of the room are out of luck. I am a physician and scientist who has studied thyroid function, including the effect of iodine deficiency and the actions of perchlorate and similar drugs in the rat and the human for more than 50 years. My strong conviction is that evaluation of the risk of perchlorate-contaminated drinking water to human health should be based primarily on data obtained in human subjects. Although the changes that occur during adaptation to iodine deficiency or anti-thyroid drugs are qualitatively similar in rats and humans, the potency of anti-thyroid drugs in humans is not always predicted by their potencies in rats. Perchlorate inhibits the thyroidal uptake of iodide through the sodium-iodide symporter. However, in both humans and rats, there can be no depression of thyroid hormone formation secondary to iodine deprivation if there is no inhibition of iodide uptake.

I and my co-investigator, Gay Goodman, performed a 14-day exposure study of perchlorate in 37 human volunteers. You may want more, but you have got to be realistic. We measured the dose-response for inhibition of thyroidal iodide uptake at daily doses of 7, 20, 100, or 500 µg of perchlorate per kg body weight. Each subject served as his or her own control.

Inhibition of uptake was linearly related to the logarithm of dose over the dose range tested, a span of two orders of magnitude. There was no build-up of effect between exposure days 2 and 14, indicating that once steady state was reached, no further accumulation occurred. We found no sex difference in the perchlorate inhibition.

Based on the observed dose-response relationship, we extrapolated that the true no-effect levels is 5 to 6 µg/kg/day, which is the amount that would be ingested from drinking water containing approximately 200 ppb perchlorate, one or two orders of magnitude greater than the contamination reported for drinking water supplies throughout the southwest. Doses below the threshold for inhibition of iodide uptake will have no effect on thyroxine synthesis. Further, there is no reason to expect that the pregnant or lactating woman, her fetus, or her infant would have a different dose-response relationship for perchlorate inhibition of the NIS than adult men and women. It may happen, but that's never going to be studied. It thus seems possible that current levels of perchlorate contamination of water supplies pose any thyroid-related human health risk.

Dan Guth, Boeing Company

I have a handout that was distributed to the peer reviewers earlier, you can distinguish by being plain white paper with plain black print. I am with the Boeing Company. Actually, if you can pull that out, I want you to refer to a figure in there, but not to the text. I'm with the Boeing Company, and I'm speaking for the Perchlorate Study Group. I'm really speaking for myself, though, because I've been doing chemical-specific risk assessments for 15 years, and really the Greer data is as good as I've ever seen it get and I want to address three issues that occur in using that data for risk assessment.

First, the intraspecies uncertainty has to be addressed. Iodine deficiency has to be considered, but the NHANES data shows that there is no iodine deficiency in the United States. Steve Lamm did a multiple regression analysis on the NHANES data and submitted it in the public comments, and it shows down to well, well below the range of what's normally considered iodine deficiency there is no effect on hormones. Secondly, thyroid disease must be considered, but the major cause of thyroid disease in the U.S. is auto-immune disease. It is not contributed to by iodine levels, especially in an iodine-sufficient population. Third, the gestational and post-partum maternal hypothyroidism is caused by several factors, two of which are increased iodine loss to the fetus and in the urine. Both of those suggest that there may be some impact of iodine insufficiency, which an uptake inhibitor might affect. The concern is reduced by the fact that the NHANES data shows essentially no iodine insufficiency in the U.S.

The second point is that the fact that this inhibition is a very sensitive precursor to the hormone change has to be addressed in the risk assessment. The figure that I have in my handout on page 2 is essentially a plot of the Greer data. It's a dose versus percent inhibition, and it also has the occupational and the therapeutic dose ranges shown with the predicted inhibition based on the Greer data. Essentially what these data show is that there has not been a

hormone change observed in the Greer study or in the occupational studies with exposures up to 0.5 mg/kg/day. So although the lowest dose that causes an effect on hormones in humans is not known, the data that we have suggest that it is probably 100-fold or so higher, or up to 100-fold higher, than the no-effect level for the iodine uptake inhibition. So, in summary, there is nothing in the literature that supports or justifies an RfD that is 100 to 200 times below the no-effect level for iodine inhibition and 10,000-fold below the effect that could have an effect on hormones.

My final point, in 10 seconds, there's a list on Table 3 in here of about a hundred different things that influence the thyroid. The biggest issue or reason for this orders-of-magnitude difference between the EPA and my conclusion is the fact that the EPA sees any change in the thyroid as being subclinical disease, when in fact the thyroid adapts to all these changes and perchlorate is an insignificant contributor.

Steve Lamm, Consultants in Epidemiology and Occupational Health

My name is Dr. Steven Lamm. I'm a physician, pediatrician, and occupational health specialist. I am the medical consultant for American Pacific, currently the only manufacturer in the United States of ammonium perchlorate. I also do contract work for the Perchlorate Study Group. Thank you very much for giving me the opportunity to try and summarize 5 years of research in 3 minutes.

I've given you a handout. The front page tells you what I'm going to say. The next thing is to tell it. Page number two demonstrates the model of human health effects over perchlorate ranges. To be understood is that perchlorate has been used for 50 years as the treatment of choice for certain types of thyroid disease, and we know a lot about it that's been published in the peer reviewed literature, on which the medical community depends.

The toxic level for perchlorate is 1,000 mg/day, which is about equivalent to the 30 mg/kg/day in the highest exposure doses. The therapeutic range, the range at which you have an effect on the thyroid, is from about 100 mg/day to 1,000 mg/day. Now, most interesting, and I submitted to you a copy of the paper by Wenzel and Lente, is that the standard way for treating hyperthyroidism is that you give a high dose to begin with, and then you try and gain control of the thyroid, and you back off to a maintenance dose. When you look at the literature, you find that the typical maintenance dose is 85 mg/day, and I hold that to be the level at which you're just having an adverse effect of thyroid hormone output. So I give you that 85 mg/day as a very important number for you to be looking at. The pharmacology group is the iodine level at which you have an effect, and you have from the Greer data that it goes down to 0.5 mg/day. In comparison, you see that the occupational exposure zone is the same as the pharmacological and does not reach the adverse effect level, and environmental is well below that.

Let's turn to the second figure. The second figure now deals with the issue of what is the effect of iodine levels in the United States on serum thyroxine levels, and you see from the

NHANES study that the thyroxine levels are steady throughout, even the low urine exposure. The third picture now deals with some of the ecological studies on newborns. It shows the relationship of the T4 level to birth weight. The reason we've done our studies at 2,500 to 4,000 is because that's where thyroxine is stable.

Offie Porat Soldin, Soldin Research and Consultants, Inc.

Thank you very much for giving me the opportunity to speak. My name is Offie Porat Soldin. I actually represent myself, but I do work with Steve Lamm and he introduced me so beautifully. I have three comments. One of them is about the TSH surge, and basically it relates to the Schwartz study. The Schwartz study gets all its data basically from the first 24 hours after birth. After birth, immediately after birth, there is a huge surge of TSH and other thyroid hormones. Therefore, the presumptive positive is actually a false positive. If you look at the bottom line, there is no increase in congenital hypothyroidism. So I would urge everybody to reconsider the data, although the study was beautifully done and the statistics, I'm sure, are great. Considering the TSH surge area of the first 24 hours is absolutely not useful. Secondly is about measurement, and I can't urge enough that, in any study, EPA studies or others, the way of measuring anything is very important, and when you pull data from several labs, if it's not the same lab that did it, it's very important to say different labs did it; one lab did it in one method, and the other lab did it in another method. If you pull all the results, it doesn't necessarily mean they are all the same. And the third thing, I was in Las Vegas myself just a month ago, two months ago, and I had no hesitation in drinking the water. I've had kids, and if I'll be pregnant again, I will not hesitate to drink the water, straight tap water. I do not believe that the levels of perchlorate in the water will do anything, not to me, and not to my baby.

Larry Ladd, Community Advisory Group, Aerojet Superfund Group

Hi, my name is Larry Ladd. I live about 15 minutes down the highway. I'm the interim chair of the Community Advisory Group for Aerojet Superfund site issues, which is an EPA-sponsored forum where Aerojet employees, regulators, and concerned members of the public get together and share concerns about whatever chemicals happen to be emanating from the Superfund site, and so the information I have to offer is in the realm of concerns, questions, and anecdotes. I do have one specific concrete correction to make to the draft risk assessment. My authority comes from having participated in creating the first document cited in the fourth chapter on ecological effects and that is the original health consultation. It states on page 4-4 that there are four cases of congenital hypothyroidism out of 11,814 births. That's inaccurate. All four of those were in the exposed zip code, and the other three zip codes basically have no perchlorate measurable at 4 ppb. And in Table 1-A of the September draft, it points out that the ratio is actually 5,217 births. That would give an incidence of 1:1,300. California is about 1:3,000; other states up to 1:5,000. You can narrow that further because in that zip code there are three separate water systems and that wasn't applied, too.

The other concerns we had were what was guaranteed to us is that the first step of the evaluation would be a fine-grained map of the thyroid data, and that map was generated. Every kid born in Rancho Cordova for the last 20 years is on a map, but unfortunately the fellow who was doing the study, Dr. Martin Hill, formerly of Public Health at UC Berkeley was laid off right before he could paste the data. So we're disappointed that that analysis wasn't here. Finally, another concern in any public issue raising thyroid questions, predominantly your concerned audience is going to be elderly women with auto-immune thyroid problems. To help address that public concern it would have been useful if some of the studies involved strains of test animals that are susceptible to the experimental auto-immune thyroid disease. Finally, the weakness of this particular study was that there was absolutely no health survey done. I went down to what I considered the apex of perchlorate exposure, knocked on the very first house, and the neighbor across the street had had [an inaudible type of] thyroid cancer. Another case of the exact same type of cancer also occurred amongst another gentleman who had moved away, who had the well in his backyard. And another family some point distant, where they grew all their own vegetables, and so the issue of bioaccumulation comes in, also suffered from the same cancer. That, of course, is just anecdote and it is not a testable hypothesis, but if you look at the incidence of that cancer in California, it's 31% in Los Angeles County, 22% in the rest of the state, and 19% in San Jose, which has comparable demographics.

David Garrison, U.S. Air Force

Hi, I actually go by Mike Garrison, and I work for the Air Force Center for Environmental Excellence, and I'm a member of the Perchlorate Working Group. Under the topics of ecotoxicology and ecological risk, I'd like to make a comment about the endpoints used to derive ecological screening benchmarks. The goal of EPA is to assess potential effects on receptors at the community or population level. The DoD's primary concern over the eco-risk component of the document centers on the choice of endpoints used to derive the screening benchmarks. In deriving an ecological screening benchmark, a requirement for endpoint selection is that it's based on an ecologically relevant effect, such as survival, reproduction, or growth. In fact, within the eco-risk arena, effects that are not clearly related to survival, growth, and reproduction of an organism are frequently argued as being irrelevant and unsuitable for benchmark derivation.

In the current document, ecological screening benchmarks for perchlorate appear to be based on endpoints with no known or implicated ecological relevance. For example, the apparent alteration in thyroid function, which serves as the basis for the herbivore dietary screening benchmark, has not been shown to result in any ecologically relevant effect. In fact, data suggests that, at the levels where the thyroid effects occur, there are no effects on development, growth, or reproduction. Another example is the use of redness and swelling as an ecologically relevant endpoint for the chronic fish assay is unjustified. At the very least, the effects of perchlorate chosen as endpoints for screening benchmark derivation should be adequately supported. In the current draft document, support of the choice of benchmarks is inadequate. If convincing justification cannot be made for current benchmark values, it's

suggested that the screening benchmarks be revised using endpoints with known ecological relevance. If no endpoints with ecological relevance are known, then there is not sufficient evidence to support the current ecological screening benchmarks.

One final comment I'd like to make on another topic, on interspecies variability, comparing rat and rabbit development studies show evidence for the magnitude of rat sensitivity to the inhibition of iodide uptake by perchlorate. However, in the rabbit developmental toxicity study, there was no statistically significant difference in the levels of T3 or TSH in dams that received up to 100 mg/kg/day. The EPA paid little attention to the dissimilar results between rats and rabbits in the perchlorate document.

Penny Newman, Center for Community Action and Environmental Justice

For the record, for those who might be curious, Roman Racca had given me his time from the California Department of Toxic Substance Control, but I want to make it very clear I am not speaking on behalf of DTSC, representing their views in any way, shape, or form, as will be very apparent, I think, as I talk.

My name is Penny Newman. I'm with the community organization in Glen Avon, California, which is the host to the Stringfellow Acid Pits, one of California's top priority Superfund sites. Even though we have over 200 major corporations that were dumpers at this site, EPA, being involved, and DTSC for well over 24 years that I've been involved with the project, not one of them have raised the issue of perchlorate. Aerojet was one of those dumpers and certainly knew about what they dumped there and that perchlorate would have been one of the contaminants to be tested for, along with the other 200. It wasn't until last summer that DTSC did any sampling for perchlorate, and have no found it throughout the community. While the plume was originally defined by TCE, which we thought we were getting pretty much under control, the area around that plume people have been hooked into an alternate water system and off of their private wells. We now find that, because of the perchlorate, that plume is more than three times what was known before. So we have an entire new population of people who have been exposed to the chemical.

In all of these instances, the corporations, EPA, DTSC have failed this community once again, and I'm wondering how many other communities around this nation are also being failed by the agencies not taking aggressive action to test for perchlorate. I wanted to kind of give a little bit, again, a reality check. I've heard that mentioned a number of times. And why I don't see the need for establishing what we consider a safe level of exposure to perchlorate, and I raise that because perchlorate is not a chemical that is added to our drinking water for any socially advantageous reason. It doesn't purify the water. It doesn't add anything to public health protection. It is simply a pollutant. It does not belong there. It clearly has identical sources of polluters. It is rocket fuel. It can be traced back to where it comes from, and under our current, which may be changed in the near future, but our current standard is that polluter pays. Or, as my mother always told me, if you make the mess, you clean it up.

I think we have enough information to know that this is a very potent chemical, and that it does not belong in our drinking water. I would hope that, as we're looking at the stakeholders in this discussion, that we include those people who you all want to study. I know human data is very appealing, but that's my family and that's my neighbors that you want to study. So please at least let us at the table, when you're discussing, at an equal level, as all of the polluters that you have listed up here, the DoD, Aerojet, and all the rest of them. We belong here to have a discussion, and you're deciding what we should be exposed to. Thank you.

Dan Rodgers, U.S. Air Force

My name is Lieutenant Colonel Dan Rodgers, and, since January of 1998, I've been the DoD team lead and a member of the Interagency Perchlorate Steering Committee executive. I like to begin my comments this afternoon by going on record recognizing the professionalism, dedication, and courage of a number of public servants, and the teams they represent. Without their vision and effort, this process would not have been possible: first, Dr. Bill Farland and his team in EPA, ORD; second, Dr. Annie Jarabek and her team throughout EPA, but especially at RTP; Kevin Mayer and his team in Region 9; Dr. Cornell Long and Ron Porter and their team at Brooks Air Force Base; Dr. Mattie and his team at Wright Pat; Jim Hurley, [inaudible], Major Jeff Cornell from Tyndall and Brooks; Larry Glidewell, Catherine McCracken, and Rachel Secada, our public relations team; Mike Girard, the chairman of the PSG and the associate members; Dr. Klaassen, and his team of professional, independent experts from the February 1999 peer review; Dr. Steve Lamm and his team at CEOH; and our state partners, including Brenda Pohlman, Bill Wallner, and Mike Honeycutt.

Throughout these last 3 years collectively, we, EPA, the member states, DoD, the PSG, and our stakeholder colleagues have taken the path least traveled in making decisions throughout the process that some may consider controversial and, more times than not, outside the partnership and research box. Our focus to get the most information about perchlorate to the American public and the relevant decision makers. We have not been afraid to make the controversial call by taking the challenge of Dr. Klaassen and the 1999 EPA external peer review, extending the information database on perchlorate by adding almost $12,000,000 in requested research. We brought the study directors for all the principal perchlorate studies, or representatives, here to answer any questions that you on the panel may have. On behalf of DoD, we prepared additional comments that we distributed to you this afternoon. DoD is also submitting more written comments to be forwarded later.

Within the partnership, our goal has never been focused on the ultimate number, but in directly making sure that, in protecting the nation from suspected pollutants, credible science becomes and remains the primary catalyst for credible decision making. Your role, as outlined in the EPA charge, is to review the Draft Risk Assessment and evaluate whether the data chosen, and inferences based on the data employed in the derivation of the assessments, are appropriate and scientifically sound. I'm proud to be in a country where two federal agencies can disagree on both scientific and policy recommendations. While our men and women in arms are fighting

a war against terrorism at home and abroad, you're here with an eye towards recommending a course of action for EPA and the nation. Do not accept the status quo. Be critical; be cautious; but regardless of any preconceived notions, apply your collective wisdom and scientific direction to this important process.

Randy Palachek, Parson Engineering Science, Inc.

Thank you for staying extra for hearing the comments. Unfortunately, just to talk about ecological, that's what I would like to focus my issues on now. A couple of quick clarifications that have come up in the recent discussion: In the Parsons study, we had over 700 or 800 tissue samples. We do have dry-, wet-weight, and percent moisture all in the original study, so that information can be pulled out. I think EPA, when they summarized it, just ended up putting in wet weights for comparisons, but the whole data is available. The other one issue when we were talking about the plant accumulation issue, I know at least in the Vegas site, where we saw the highest plant accumulation in the leaves there, the groundwater is very shallow there—and it's within 6 inches of the surface. So, you have to know and look at the soil concentrations to see what the concentration is in the tissues, but also the groundwater should be looked at as well.

A couple other quick comments I'd like to make is, we are currently—to let everybody know, all the interested parties—working on an Air Force study, where we are collecting seven additional species for ecological toxicity. One of those is an earthworm study, and that is just about wrapped up. Our preliminary numbers indicate that they do not bioconcentrate perchlorate, either, having less than 1 BCF. In addition, we have [inaudible species name] clam, for a bioconcentration study from the aquatic side, and [inaudible species name] sunfish species; and both of those indicate that perchlorate is not bioconcentrated in the tissue in the laboratory studies. In addition, we are accomplishing with those two species and four other species, including [inaudible species names], rainbow trout, and [inaudible species name], additional aquatic toxicity studies. And those should be finished up within the next few months. We hope to have a report out in the June–July timeframe that will have all the data in it. It will be GLP, and it will be measured concentrations and not just nominal.

All this data will be used to develop a surface water quality standard, using the EPA protocol. We are working with several state agencies, as well as a few EPA regions, to develop that surface water quality criteria document that will be available for all parties to use in the risk assessment purpose. With that, I'll just wrap up and let Ron Porter, who collected some of the data in the Parsons study, address anything else that might come up.

Richard Garrett, City of Waco

Thank you. I'd like to applaud the efforts on the committee and EPA on this issue. I'm with the City of Waco water utility department, and we provide water to about 130,000 people, and there's just a couple of points I want to make. The Texas Tech study, a lot of the work that

was done, is in our watershed. We are growing at about 9% per year, and our watershed, along with that of Lake Belton, which serves another 300,000 or so people in total, is also affected. So, the two points are: while we're deliberating on what is acceptable risk and making sure the science is sound, the exposures are continuing. Through groundwater and surface water, we have some exposure from a former munitions plant that is being decommissioned, and so this work—if I don't have to tell you all—is very critical. The other issue is the lack of data in the study on the ecological assessment. I think the Tech work, if you haven't reviewed that, I think it fills a lot of the gaps that were identified. It certainly makes it a lot more comprehensive, and I just appreciate your work, and give your time back.

Douglas Wahlsten, University of Alberta

First of all, I'd like very much to thank the peer reviewers for this opportunity to address you in person. I know several of you all read some of the comments I've made. My specialty is the study of genetic variation and sex differences in the corpus callosum of mice, rats, and humans. I've worked on this for about 30 years. I've looked at thousands of corpus callosums of these species. I've also created strains of mice that have no corpus callosum—it's a hereditary condition. My current work, I'm working on a mouse [inaudible] project, and my laboratory in Alberta has been chosen as the site to develop or to obtain standard morphometric data on the mouse brain, including the corpus callosum and other fore-brain commissures, for a large number of inbred strains of mice. So, this is sort of the main thing we do.

I have to tell you, tell the committee, that I do have prior involvement with perchlorate. After the Sputnik went up, I, and a lot of the students in my neighborhood, we actually began to build small rockets and launch them, and a number of these were actually fueled by perchlorate. That's the extent of my knowledge, and I ask that you not tell my parents about this. They might be a bit upset.

So, onto the brain morphometry, Toxicology Excellence for Risk Assessment asked me to review the data from the Argus 2001 Effects Study. I was provided with the raw data and also with scanned images of the brains. In my opinion, the morphometric measurement methods that were used in these studies are seriously flawed and very much prone to artifacts in the way they made the measurements. Linear measures of the corpus callosum in the hippocampus simply do not achieve the acceptable standards in neuroscience today. What we need are areas of these structures measured in cross-sections. In the case of the corpus callosum, it's very simple. You cut the brain right down the middle, and then measure the size of that structure in one section. That's all you need, one.

I would not rely on a coronal section—a single coronal section—even to tell me if a corpus callosum is 50% of its normal size. If it's absent, sure; but if it's reduced by 50%, I would not rely on a single section. You have to cut it down the middle, and everybody in the field does that. I do feel that there has been more time and money spent in debating this issue than would have been required to do the whole thing correctly in the first place. When you look

at the data, and I went back and looked at it recently, sadly there is a serious bias in those data, and the EPA conclusions about the post-natal day 21 rats are sadly based upon an artifact and I urge the EPA strongly to remove that part from their report. The plane of sectioning is not comparable, and it occurs in particular groups that leads to the inverted U-shaped function.

Ronald Porter, Mitretek Systems

Thank you very much. My name is Ron Porter, and I'm a biologist with Mitretek Systems. My conflict of interest is that I'm a former employee of the U.S. Air Force and was one of the principal architects and field ecologists for the bio-transport studies. So, I'll take any applause or blame for the outcomes of those studies. Earlier in the day, I heard some discussion about how to weight the human health studies and human health outcomes with that of the laboratory data, and I think we see a similar circumstance with ecological data, because if you are in the field and you are at locations with known perchlorate contamination, you do not see the types of perturbations that you might expect with similarly exposed laboratory animals.

I would like to report some of the observations that were made at Lake Mead. It's our most contaminated site. The contamination at Lake Mead began probably 50 or 60 years ago, at the end of World War II, with the manufacture of perchlorate. By today's measurements, if you look at concentrations of perchlorate in Lake Mead and in the Colorado River as far south as Yuma, and you do the mass calculations, it would have to be literally tons of perchlorate that would have to pass through the shallow groundwater and into the Las Vegas Wash. And our observations there, and Dr. Adams presented some of the data, the highest concentrations in soil, the highest concentrations in groundwater, the highest concentrations in tissue coincidentally were also found at the sites where our trapping success and collection success was the highest.

For mammals collected in the area, our trapping success was absolutely the highest. You could walk down the trap line, bait the traps, and, on the way back, you would hear the traps slam shut. Coincidentally, that's also the sites where there were highest concentrations of perchlorate in the plants and in the soils there. Likewise, for [inaudible species name]—the mosquito fish—Annie always likes for me to have at least one genus and species in my talks—for the mosquito fish, in the areas of the seeps where the concentrations of perchlorate were the highest, so high in fact that the electroshockers could not generate a current in the water, the numbers of [species name] that were there were also the greatest. So you could actually take a dip-net and scoop those things up.

I would also like to comment on some of the data that was discussed earlier related to the *Xenopus* assays. I know that Jim Carr's done some great work with some of that and provided some great information. There's also some data out of Jim's lab that reports that site-contaminated water that's brought into the lab and the *Xenopus* assay used with that has not been able to duplicate the results that are seen in the lab using regular lab water and the regular *Xenopus*. Thank you.

LaDonna White, Capitol Medical Society

Good evening. Thank you very much for your time and attention. My name is Dr. LaDonna White, and I represent the Capitol Medical Society, an affiliate of the Golden State Medical Association. We are the largest association of African American physicians in California. I am here today because the Capitol Medical Society and Golden State Medical Association are vitally interested in ensuring that appropriate risk assessment methodology is used to establish a reference dose of perchlorate.

Our concern stems from observations as physicians and as committed members of an underserved community. What we are seeing is extremely conservative risk assessment practices that result in very costly treatment and remediation actions. Far too often, these risk assessment practices and findings are distorted by various interest groups who deliberately mislead and scare the public. The result is the diversion of public and private dollars into unnecessary risk management efforts and away from more immediate, real and dangerous health related programs.

Yes, I am aware that your task is to look only at the science behind the draft reference dose for perchlorate. Yet we must consider the impact of our decisions and actions on health challenges that face us today, at this moment. As detection technology improves, more resources are devoted to removing smaller and smaller amounts of elements from our drinking water, yet at a price that takes dollars away from our communities and our ability to address very real health concerns. In a time of severely restricted local, state, and federal budgets, we must be very careful on choosing those problems upon which we commit our limited financial support. Indeed there is a cost of being extra safe by adding uncertainty factors and deciding to provide overly stringent parameters on our findings of no observable adverse effects. Let us not create phantom health threats where valuable resources provide no real reduction in risk to public health.

Here are a few examples of real health issues affecting the African American community—issues that can reap substantial public health benefits if significant public financial resources are directed their way. The infant mortality rate is more than twice as high for African Americans than for whites. The African American death rate due to diabetes is more than twice that for whites. African Americans are 30 percent more likely to die from heart disease than white Americans and 30 percent more likely to die from cancer than are whites.

There is only so much money, and there are so many needs. I hope you will keep in mind the high cost of being extra safe, and the missed opportunity to spend money on health issues that will have the most impact on the health of the minority community in California. Thank you.

Jonathan Borak, Yale University

I'm Jonathan Borak. I'm a physician and a DABT toxicologist. In the school of medicine, I teach toxicology, and I teach risk assessment. I am here on behalf of Lockheed Martin, and, in the interest of everybody else, I'm going to make only one point. I would like to first, however, thank EPA and ERG for the opportunity to be here, and I thank all of you for your incredible patience and tenacity, not only for sitting here all day, but for also the amounts of reading I know you've all done, because many of us have done a good bit also.

I would like to talk to one particular issue that was raised earlier, but I'd like to reinforce it, if I may. The risk assessment relies on a LOAEL generated out of four rodent studies. Those were the Argus 2001, the Argus 1998a, the Springborn 1998, and the Bekkedal 2000. I apologize if I've mispronounced your name. There's a critical issue here, which has to do with confounding. I would rather be talking about human health, instead of rodent health, but the fact is, when speaking of human health studies, I heard a great deal of concern about confounding—confounding lack of information on cigarettes, or lack of information on birth temperatures, and lack of other kinds of concerns (body weight).

The effect of confounding by the choice of chow that was used—the dietary basis of these studies—is so extraordinary, and the fact that it has not been brought up more, and more succinctly and clearly, I feel that an enormous error and an enormous need for you to address it. Argus' two studies and Springborn used a Purina chow 5002, and the Bekkedal study used Techlab-certified rodent diet. Both of those are proprietary and it was not possible for me to get the actual breakdown of constituents, though, if you call or ask, you can easily get the quantity of isoflavones in them. Both studies, particularly the Purina chow, has been specifically studied because of its endocrine disruptive effects, not because of its thyroid disruptive effects. It is also a phytoestrogen.

And it is a concern, however, and in my discussions with the manager of specialty research at Purina, [name inaudible], that the concern about the potential thyroid interactions is something that Purina is aware about, and they have simply said, and I have offered you the cite in my submission that was written, that synergism with perchlorate and that diet should be expected. Soy is goitrogenic. It's been known since the early 1950s that pure soy diets cause hypothyroidism and goiter, but the most impressive data is actually from [name inaudible], published in *Carcinogenesis* in the year 2000. We are looking at a diet of gluten versus soy. Gluten has no isoflavones. We are looking with and without iodine. The effect of soy and iodine depletion is enormous. It is more than additive; it is multiplicative. And I believe this data invalidates the extrapolations made in the four studies that are the relying point for the LOAEL, and it would be so readily simple to simply reproduce, with these dietary manipulations, to determine whether that data is usable. I thank you very much. I appreciate the opportunity to be here.

Sujatha Jahagirdar, CALPIRG

Thanks very much. My name is Sujatha Jahagirdar, and I am CALPIRG's safe drinking water advocate. CALPIRG stands for the California Public Interest Research Group. We are one of the largest environmental and consumer watchdogs in the state of California. We have 70,000 members and are part of a national network of state PIRGs.

The purpose of today's proceedings, in my view, is to try to decide how much rocket fuel is safe to drink. My critique of the proceedings today rests on those who haven't been at the table to help make this decision. CALPIRG believes that the most important constituency in making this decision is the millions of men, women, and children that have been unknowingly drinking rocket fuel for decades across the country. As the proceedings went on inside this hotel today, communities across California, including Rancho Cordova, the San Gabriel Valley, San Bernardino, Chino Hills, the list goes on, are grappling with the consequences of this massive public health and regulatory debacle by going to the doctor for thyroid problems, rare forms of cancer, and aplastic anemia.

CALPIRG does not believe that those entities that have been identified as responsible polluting parties, and those entities that they have funded, should have an equal voice at the table in deciding the outcome of these proceedings. Since public representation has been so lacking today, I would presume to speak for the average community member with whom I've been working with for the past several years in answering what I see as the fundamental questions that have been raised here today. Question number one: Are there major health concerns from drinking perchlorate raised in this EPA draft toxicological assessment? The answer, in my view, is yes. Do I want to be drinking it? The answer is no. Do I want my unborn child exposed to it? The answer is no.

CALPIRG believes that the EPA and relevant regulators should move as quickly as possible, based on the answers to these questions, to [a] get rocket fuel out of our drinking water supply completely, [b] make sure that polluters pay completely for cleanup, and [c] prevent further contamination. Thanks very much.

Paul Winkler, Acculabs, Inc.

Good morning. My name is Paul Winkler. I'm the director of specialty analytical services at Acculabs. Acculabs is a contract analytical laboratory in Golden, Colorado. Our interest in perchlorate analysis came about because we have several clients who had a need for perchlorate analysis, but their data quality objectives were not being met due to limitations with the current ion chromatography method. These limitations were primarily based on a lack of sensitivity, rendering high detection limits, and a lack of specificity, giving rise to potential for false positives.

This led us to get involved in a study with the Department of Energy, in the Albuquerque operations, where we studied water that was spiked at 4 ppb. Using the ion chromatography method, we found that, at 4 ppb in the blanks, we got a 20% rate of false positives, which is an indication of a lack of specificity. Then, in the waters that were spiked at 4 ppb, we got a 20% false negative rate, and that's due to a lack of sensitivity in the method and a difficulty in actually identifying a peak. This led us to develop an LC/MS/MS method—that would be liquid chromatography/mass spectrometry/mass spectrometry. This method is far more sensitive and far more specific than the current ion chromatography method. With our method, we were able to get a detection limit of 50 parts per trillion for perchlorate. That was arrived at by spiking an actual groundwater sample from a deep well from west Texas at 250 parts per trillion, and we analyzed seven samples and received 112% recovery, which gave rise to the calculated MDL of 50 parts per trillion. Similarly, we spiked a sandy soil at 5 µg/kg, and we ran seven samples with an average recovery of 114%, which gave rise to an MDL of 2 ppb.

So, yesterday's speaker, the last speaker of the day, indicated that he wanted a method with 1 µg/L for waters and 10 µg/g for soils, and I would say that that method is here today. We have fully validated the method from 0.25 ppb up to 20 ppb. And the last comment I'd like to say is that it's not only more sensitive than the IC method, but it's also more specific. For us to have a false positive identification, the compound would have to have the same retention time as perchlorate, form a negative ion at the molecular mass of perchlorate, fragment to the daughter ion of perchlorate, and also form a negative ion. And that's not very likely. So, in conclusion, I'd like to say, I believe that we have the analytical methodology present today to do these analyses at lower levels for environmental monitoring. And I would like to thank ERG and the Agency for allowing me to speak this morning. Thank you.

David Mattie, Air Force Research Laboratory

First of all, I'd like to thank you for the opportunity to make these comments. First of all, on the transport of perchlorate into thyroid cells, AFRL HEST would like to point out that evidence to support the uptake of perchlorate into the thyroid exists, and the AFRL studies by Yu et al.2000a and 2000b, which are iv and drinking water studies, when NIS was up-regulated in rats, thyroid perchlorate concentrations also increased, as well as iodide. Cold perchlorate was measured in the thyroid of rats in these studies using ion chromatography, a modification of the EPA Method 314. This method is selective for perchlorate. We checked for chlorate and chloride in the thyroid and confirmed we were looking at perchlorate and not metabolites.

Perchlorate is concentrated in thyroid. We saw thyroid to serum ratios between 10 and 30 in the male rat in drinking water studies at doses from 0.1 to 10 mg/kg/day. In fact, PBPK models can predict these up-regulated levels quantitatively, when the model assumed that NIS upregulation maintained the iodide uptake in the presence of perchlorate competitive inhibition. In a 3 mg/kg study, 93% of the dose was excreted in 24 hours. On analytical issues, the matrix is an issue with HPLC method for perchlorate. The sensitivity is reduced in blood, urine, milk, and rat tissues, but you can still separate the perchlorate peak without any interference, because the

sample preparation we developed for biological matrices. In the 90-day perchlorate study by Springborn Labs, it was a Hamilton-Thorne IVOS-10 semen analyzer that was used for the sperm parameters.

On the use of human data, we've heard a lot about the inconsistencies in the animal data, especially because of the soy products in diet. This further supports the use of human study. There are concerns about the use of the Greer study. However, the Crump study in Chile looked at the critical effect: T3/T4 in children and TSH in newborns. A reference dose could be developed from the Crump data that would be similar to the RfD for the Greer study, showing that both the human clinical and epidemiological studies are mutually supportive. We recently received the blood and urine samples from the Crump study. In an initial analysis just completed, we can detect perchlorate in the blood and urine. Blood levels are approximately what the PBPK model predicted. Furthermore, a follow-on study will start shortly looking at pregnant women in the same three cities in Chile. Perchlorate will also be measured in blood, urine, and milk. I feel you don't need to wait for this study to use the Crump study now for the development of an RfD. The results will serve as further validation of the human data.

To end with some questions for the panel: Is the Greer study compromised by scientific limitation, such that it can't be used for risk assessment? Is it reasonable to conclude that the rat data is a more reliable basis for human health risk assessment for perchlorate? Is there any reason that a dose below the NOAEL for iodide uptake inhibition would cause any risk? And finally, we would ask that you provide definitive comments and clear conclusions back to EPA to help us solve controversial scientific issues, rather than simply identifying the issue. Thank you very much.

John Gaston, Alliance for Responsible Water Policy

Thank you very much. Good morning. My name is John Gaston. I believe you've got a copy of the comments that we've made here. I'm here today in my capacity as the Executive Director of the Alliance for Responsible Water Policy, a coalition of water-related institutional and business organizations that's been engaged in the area of drinking water quality issues in California since 1995. I've got almost 40 years experience in the drinking water and public health area—20 as a regulator with the United States Public Health Service and the California Department of Health Services, and 20 as a consultant. Along the way, I served for 12 years on the U.S. EPA National Drinking Water Advisory Council, 5 years as chairman.

The alliance that we represent here today exists for the purpose of ensuring drinking water safety standards are based on the best available science. I'm here today because the Alliance for Responsible Water Policy is vitally interested in ensuring that appropriate scientific methodology is used to determine the U.S. EPA's reference dose for perchlorate, and that's where we're going to end up is with a drinking water standard. As an aside, not in the remarks, there are two sea changes that we have seen in the drinking water utility business that dramatically affect what we will do here today. Number one is that consumers are increasingly concerned and increasingly

aware of drinking water quality issues and that includes the realization that drinking water actually does contain compounds other than hydrogen and oxygen. And the second is that lawsuits involving drinking water utilities are increasing exponentially. This magnifies the need for good science and balanced interpretation on your part, and those that will follow after you.

Throughout my professional life, I have represented drinking water quality professionals and advocated the furtherance of public health in the water utility industry. These are the men and the women on the front line that have to implement the standards and have to protect the public from water-borne disease or water-borne illness. What concerns more and more the drinking water professionals is the use of ultra-conservative risk assessment practices that are not necessarily based in sound or complete science and that may result in extremely cost treatment and remediation burdens. Far too often, these risk assessment practices and findings are misunderstood by the public and, worse, distorted by various interest groups. This is often a regrettable and an entirely avoidable and uncalled for loss of confidence in the public drinking water systems and diversion of public health and private dollars.

I'm well aware that your task today is here to look at the science, but you must also consider the policy implications involved in that, and that comes at a high price. Interestingly enough, of the 14 people that spoke yesterday, I thought that it was very interesting that, of the 11 that had what I consider to be credible scientific experience, they were relatively unhappy with some parts of the document, and I would share that there are some scientific concerns involved with that. I'm going to conclude at this point to urge the peer review panel to take a close look at the human data—we, too, believe the human data is important—reported by Drs. Greer and Goodman at Oregon State and others in the review of the reference dose. The outcome of your deliberations here will have an enormous impact on the lives of everyday Californians and, sadly, we are not sorry about being overly cautious in this matter. Thank you very much.

Gilbert Ross, American Council on Science and Health

Good morning. I'm a physician and Executive Director of the American Council on Science and Health. ACSH is a consumer education organization—a consortium of 350 physicians and scientists from throughout the country concerned with issues related to nutrition, chemicals, pharmaceuticals, lifestyle, and the environment. We were founded in 1978 by a group of scientists who had become concerned that many important public policies related to health and the environment did not have a sound scientific basis. It is with this mission in mind that we turn to the perchlorate issue in an attempt to help guide the EPA to adopt a scientifically sound and appropriate reference dose for perchlorate and to address misrepresentations that have been associated with this debate.

In January, we published a special report. We commissioned a toxicologist, Dr. Daland Juberg, to write this report for us. We were attracted to this issue because of certain alarmist scares that had been released into the media. The American Council on Science and Health is

vitally interested that an appropriate risk assessment methodology be used to establish a reference dose for perchlorate, because too often overly stringent regulatory approaches to trace levels of environmental contaminants place onerous financial burdens on local governments and industries, with little or no public health benefit ensuing. We must avoid diversion of scarce health resources away from areas where they are otherwise desperately needed. We believe that a thorough review of the available science will demonstrate that the draft RfD of 1 ppb is far too conservative.

The collaboration among the EPA, the Department of Defense, and the interindustry Perchlorate Study Group is unique over the past several years. Their findings ought to be given great weight as you evaluate the adequacy and the scientific soundness of the EPA's conclusions and draft RfD. Because of our mission to identify significant public health threats and to distinguish these from non-significant to non-existent scares, using sound scientific analysis, we highlighted some of the recent scientific studies that have further characterized the toxicity of perchlorate in animals and humans. We wish to avoid what we believe to be ultra-conservative environmental exposure levels and give due weight to extensive amount of toxicological data, including reliable human and animal studies that have been generated in the last few years. We anticipate the final RfD will be scientifically supported, as well as any other regulated chemical in commerce today.

In conclusion, I urge the peer review panel not to be overly cautious in evaluating the newly-proposed RfD for perchlorate, bearing in mind the ramifications and unintended consequences of doing so. We have accumulated much new data on perchlorate over the last few years, so the RfD, we think, should be higher than the prior mark. The latest human studies especially support a higher RfD as a safe exposure level. Unnecessary expenditures and needless remediation of a non-problem is unwise policy. As our analytic techniques get more and more sophisticated, we will be able to detect thousands of chemicals at trace levels. If we attempt to purge them all down to zero, under the [inaudible] of better safe than sorry, we will have precious few resources left for other urgent public health needs. Thank you.

John Gibson, American Pacific Corporation

Thank you for the opportunity to comment. My name is John Gibson, and I am CEO of American Pacific Corporation. We are a small business manufacturer of perchlorate chemicals. We have made perchlorates since 1958. Therefore, we have a vital interest in the outcome of this risk assessment and the subsequent regulatory process.

I recognize that this exercise today is a technical peer review of an assessment which will form the basis for determining justification for regulation. I should not be here to question the process or the administrative decisions which have resulted in the content of this document. However, the administrative process has, in fact, determined what you will now review and the emphasis given the various scientific studies contained therein. Sadly, the review and risk assessment is incomplete and dismissive.

In mid-December of last year, the Agency adopted an interim policy which states in part that "the Agency will not consider or rely on third-party studies involving deliberate exposure of human subjects." This policy unnecessarily restricts your ability to fully assess the risk of perchlorate exposure on human health. For example, the study authored by Greer, Goodman, Pleus, and Greer, the so-called Greer study, although referenced in the risk assessment, is effectively dismissed: "the human clinical studies have significant scientific technical imitations that preclude their use as the basis for a quantitative dose-response assessment." We respectfully disagree and find this conclusion surprising in light of the fact that the Agency assisted in the design of the study protocol.

Other work by Lamm, Braverman, Crump, Gibbs, Lawrence et al. is similarly dismissed. Since the Greer study identified a no effect level in water (concentration of 200 ppb) for the key event in mode of action analysis, we are more than just disappointed with the risk assessment's treatment of this and similar work. In fact, K.S. Crump calculated in an occupational study of the highest exposure group in the country that a safe work place exposure level would be 50 to 60 mg/day, which is equivalent in water concentration to 20,000 to 30,000 ppb. In plain words, the interim policy adopted by the Agency is dumb, and it is dumb because it deprives the EPA of the best available information—information that other agencies, such as the FDA, use in their deliberative processes.

Since 1997, our company alone has spent over three million dollars in funding human health studies and in characterization work. Always it has been our objective to protect our employees, preserve the environment, and assure our 211 employees, their families, our customers, suppliers, shareholders, and the community in which we work that the product we make is safe. The data and conclusions of these human health studies support our belief that the reference dose could be safely set at a higher level than indicated in the subject review and risk characterization. Thank you.

Mick Major, U.S. Army

Good morning. I'm with the U.S. Army, USA CHPPM. We're a health branch of the Army. We're not in restoration. We report directly to the Surgeon General. We try to assist in things like this when we can. I read this risk assessment for the first time about 4 or 5 weeks ago, and I thought it really was a beautiful piece of work. I thought it was elegant. I thought it was well conceived. I liked the idea of planning ahead, getting the tests done. I liked the idea of including the cancer with the noncancer endpoints. There was an awful lot that I really liked about it. I didn't realize there were some problems with the rodent data until I came to this meeting, and I realize that it's still going to be a toss up and that data may still be used.

So what I'd like to talk about just for a second is the use of the 3 uncertainty factor for duration, the cancer effect. I understand why using the rat data for morphometry was necessary. Obviously, we can't be cutting up human brains. And I understand why a 3-fold factor would be used for duration if you only used the rodent data, because the NOAELs of the developmental,

cancer, and the morphometry were very close—the LOAELs, excuse me, were both very close—there wasn't NOAELs. So, the NOAELs may actually have been overlapping, so I understand why the 3 was used. However, there's no reason not to use human data for the cancer effect. We have an awful lot of human studies and also epidemiological studies. They're negative for the cancer effect. Now, if we look at the human populations who are receiving perchlorate and they're not having sustained increases in TSH—I understand that there's a transient increase, but if the increases are not sustained—they're not getting the hypertrophy and the hyperplasia, we can safely say that these populations are not going to have a significant increase in the incidence in the thyroid cancers.

Now, because we have the human data, there isn't an effect, and I think if we look very closely at the human data now and see if the TSH is elevated and see if we're getting the hyperplasias, and if we're not, I think we ought to absolutely eliminate the factor of 3 from the risk assessment. Thank you for your attention.

Renee Sharp, Environmental Working Group

I'm here representing the Environmental Working Group and also the California Public Interest Research Group, which are both research and advocacy organizations working on public health issues. Perchlorate was detected in groundwater in 1957 for the first time. Forty-five years later, contamination has been found in 20 states, and the true extent is still unknown. The first perchlorate reference dose was proposed in 1992. Ten years later, we are still waiting for an enforceable drinking water standard.

The EPA's newest proposed reference dose is a step in the right direction, but it is still not sufficiently protective. Briefly, EWG and CALPIRG have concerns about the use of a composite safety factor of 300, given the high incidence of hypothyroidism in the general population, the progression of effects seen at longer exposure durations, a lack of any truly long-term studies, and the use of a LOAEL versus a NOAEL for RfD derivation. EWG also notes that an equivalent drinking water standard of about 0.2 to 1 ppb would provide only a minimal margin of safety, if any, given Schwartz's finding of a thyroid hormone change in California infants born to mothers who consumed water with only 1 to 2 ppb perchlorate during pregnancy. Furthermore, EWG continues to object to the use of adult drinking water consumption values and body weight values for the calculation of a hypothetical drinking water standard, and would like to see some discussion of this among the peer review panel.

It is clear that many scientific questions remain about the toxicology of perchlorate, and there probably always will be, but the people and communities who are being affected by contamination, knowing or unknowingly, cannot afford to wait another decade for further study. There is a sufficient body of research now, and EWG and CALPIRG encourage the EPA to expedite the standard setting process. Finally, I'd like to take a moment to remind the peer reviewers that, in matters of public health, if we are to err, let it be on the side of caution. The people and communities with perchlorate contamination don't care that a tumor is reversible,

that their babies' thyroid hormone levels may only be affected a little bit, that the iodine uptake by their thyroid is depressed by just 20%, or that the changes in brain section sizes—I've seen it in rats—may not have any effects that are immediately apparent. These people do not choose to be drinking rocket fuel and, to them, any amount of risk is too much. Thank you.

Peter Rooney, Rooney Group

Good morning. My name is Peter Rooney, and I'm the former Secretary for Environmental Protection in the state of California. I'm appearing here today at the request of several business clients. My experience is not in the area of science, but rather in the realm of public policy. Your task today crosses both fields. Many will say your task is purely scientific, but I submit that the document that you are asked to review is flawed because of public policy positions incorporated by U.S. EPA.

EPA adamantly complains about the lack of knowledge and about the acts of this chemical, yet they refuse to incorporate the data from human studies, such as that of Drs. Greer and Goodman. I submit as your role to separate science from these public policy positions, and determine if the conclusions reached are scientifically sound in light of the body of knowledge that does, in fact, exist at this time. EPA would generate greater public confidence in their work, if they would emulate President Bush. The President was faced with a similar ethical decision concerning research based on stem cells. He chose a more sensible course. He did not bar the use of the existing stem cells. He decided the existing stem cells should be used to further the world's knowledge base, but then no further stem cell lines should be developed with federal funding.

U.S. EPA, in this case, made a different decision. They chose ignorance over knowledge. They decided to ignore existing human data. They then decry the lack of knowledge and call for an increase in the previous 100-fold uncertainty factor to the proposed 300-fold uncertainty factor. I call upon you to consider the short-sightedness of this approach. I call upon you to ask that EPA consider the body of the world's knowledge in determining a realistic reference dose.

EPA further tells us that this proceeding is not about management. They assert, and I quote: "An RfD would only be one step in the future regulatory process of determining, based on a variety of elements, whether a drinking water standard for perchlorate is appropriate." I suggest that this proceeding, in fact, is the very foundation of risk management. If policy makers are given a flawed number, they will devise a flawed response.

Subsequent proceedings must start with confidence in the expression of hazard. You are being asked to add your voice to confirm the public policy determination that a 300-fold uncertainty factor is necessary. You are being asked to confirm two public policy decisions: one, that some existing human research is inappropriate; and two, that this self-inflicted ignorance results in the need for a 300-fold safety factor. If you are wrong, if the number is overly conservative, public policy is not well served. Affected parties will be subject to

increased anxiety, and responsible parties will be called upon to meet overly-ambitious remediation goals. Over the long term, numbers that have no grounding in reality tarnish the credibility of the full range of the program. And let me conclude by saying a house that is built on a shaky foundation will surely fall, and I'm afraid you are being led down to that shaky foundation. Thank you very much.

Gideon Koren, Hospital for Sick Children (Comments faxed to the meeting and read by Steve Lamm)

Hello. First of all, I'd like to thank you for giving Dr. Koren the opportunity to be spoken for. He says: I speak to you in the context of the EPA review of environmental perchlorate exposure, as it may affect thyroid function *in utero* with potential long-term neurobehavioral effects on children. I'm a pediatrician toxicologist at the University of Toronto. In 1985, I founded the Mother Risk Program, which councils pregnant women, their families, and health professionals on the risks of drugs, chemicals, radiations, and infections during pregnancy and lactation. In addition to conducting our human research, we systematically review the cumulative world knowledge as pertain to human teratogenic exposure. Presently, we council up to 200 cases a day.

I am concerned with EPA putting a lot of weight of the recent PhD thesis of Schwartz. From a clinical standpoint, it is not reasonable to compare indices of thyroid function during the only day in life when they are known to be all over the place. Any statistical attempt to correct for different times of obtaining these tests is bound to make assumptions on mean changes over time. This is especially critical here, because the groups are not evenly distributed. This is important because papers looking at later measurements come to different conclusions.

Not surprisingly, there is no correlation in Schwartz's work between presumed intake of perchlorate, based on postal code, and congenital hypothyroidism. At exposure levels presumed to happen in these regions of California, there are no known adverse effects in animal models tested. Human studies of thyroid drugs—PTU, methimazole, [inaudible drug name]—show effects in newborn thyroid function and also, in some instances, on neurodevelopment. As expected, exposure levels in these human studies are those causing measurable effects in the mother. However, studies showing *in utero* thyroid hyperplasia from anti-thyroid drugs failed to show long-term effects on neurodevelopment (see *Prenatal Diagnosis* volume 220, etc.).

Additionally, there are three neurobehavioral studies, now in various stages of publication, that have been submitted to you in the public comments. All of these failed to show neurobehavioral effects of environmental perchlorate in typical levels encountered in the environment. I am sure you receive input from different experts. I hope you will have the wisdom to listen to people whose expertise in human *in utero* exposure, so that there is a meaningful context for the animal data. Sincerely, Gideon Koren, M.D., Professor Pediatrics, Pharmacology, Pharmacy Medicine, and Medical Genetics, University of Toronto. Thank you.

Appendix I

Copies of EPA's Opening Presentation Materials

Perchlorate Environmental Contamination:
Toxicological Review and Risk Characterization
External Scientific Peer Review
March 5 & 6, 2002 Sacramento, CA

United States Environmental Protection Agency

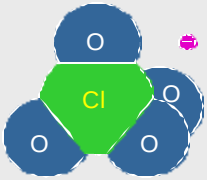
Office of Research and Development

Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization

External Peer Review Workshop
Sacramento,CA
March 5 & 6, 2002

Opening Remarks

Herman J. Gibb, Ph.D.
Acting Associate Director for Health
National Center for Environmental Assessment



Perchlorate Contamination

- Issue identified by Region 9 in 1985
- Appreciation of widespread nature emerging with improvement in analytical methods and occurrence surveys
  - Method 314.0 for detection in water developed
  - Placed on CCL and UCMR
- Integrated approach required:
  - Analytical detection methods in various media
  - Occurrence / exposure / transport & transformation
  - Health and ecological risk assessments
  - Treatment technology
- Revised risk assessment in response to 1999 external peer review

Perchlorate Environmental Contamination:
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March 5 & 6, 2002 Sacramento, CA

Pro-Active Partnership

Department of Defense
AFRL
Perchlorate Study Group

PSG

ORD
OW
OSWER
Regions

NIEHS

NIOSH

Interagency Perchlorate Steering Committee

I P S C

IRIS Peer Review

- Integrated Risk Information System (IRIS) is Agency database for risk assessment estimates
- Independent contractor (ERG) charged with finding scientific experts in needed areas
- Document provided on web January 18, 2002 with an accompanying CD of gray literature available upon request
- This is a ***DRAFT*** risk assessment and not a rulemaking
  - Premature to interpret these draft risk estimates as final EPA conclusions
  - Ample future opportunity to comment in proposed rulemaking process according to legal, regulatory or policy requirements of programs

Perchlorate Environmental Contamination:
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Purpose of IRIS Peer Review

- Provide peer review of protocols, performance, and results reported in studies since 1999 that have not appeared in the open literature
- Provide individual expert comment on EPA external review draft regarding approach, analyses, and inferences used in the human health and ecological risk assessments
  - Panel is ***NOT*** charged with arriving at a consensus opinion or conclusion
  - Public and observer comments incorporated according to professional judgement of panel
  - Comments related to EPA policy or potential rulemaking are ***NOT*** relevant to scientific review

Risk Assessment Closure

- Public comment period extended until April 5, 2002
- Draft peer review report back to the panel and to the Agency on April 22, 2002
- Final external peer review report May 22, 2002
  - Posted on the EPA web in June
  - Agency is responsible to respond to comments
  - Disposition of major comments will be indicated in final document
- Submit revised final draft document to IRIS Agency consensus review in summer 2002
- Final changes in response to Agency review
- Expect IRIS clearance with final document posted to IRIS in fall 2002

Future Steps: Regulatory Readiness

- No National Primary Drinking Water Regulation (NPDWR) at this time
- Draft ORD 1999 guidance will stand until new assessment finalized
- CCL Research Priority in All Areas:
  - **Health:** Develop reference dose (RfD) as risk estimate
  - **Analytical:** Method 314.0 for water, extend to other media
  - **Treatment Technology:** Cost and efficacy by end use (e.g., drinking water versus agricultural)
  - **Occurrence/Exposure:** UCMR and other surveys
- Near term: Use "RfD" to develop a health advisory (HA) under SDWA general authority
- Evaluate progress in each area for "go" on maximum contaminant level goal (MCLG)

Future Steps: Regulatory Readiness

- Determine to regulate perchlorate as a CCL contaminant under SDWA
- Timing based on evaluation of "meaningful opportunity for health risk reduction" based on sufficient health effects and occurrence data
- Development time frame
  - If determination to regulate is made, the agency has 24 months to propose a NPDWR and 18 months to finalize
- Considerations of additional risk management factors:
  - Analytical methods
  - Treatment technology capabilities
  - Cost and benefits

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The Perchlorate Contamination Challenge

Credible Science

Credible Decisions

- Accurate risk characterization
- Appropriate management strategies

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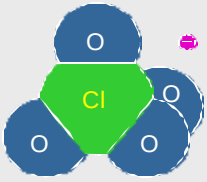
Background and Assessment Highlights

Annie M. Jarabek
Special Assistant to the Associate Director for Health
National Center for Environmental Assessment



2002 Risk Assessment Authors

Randy Bruins, Ph.D.*
Harlal Choudhury, Ph.D.*
Tim Collette, Ph.D.
Kevin Crofton, Ph.D.*
Vicki Dellarco, Ph.D.*
David B. Dunson, Ph.D.
Andrew Geller, Ph.D.*
Michael Griffith, Ph.D.
Jean Harry, Ph.D.
Brian H. Hill, Ph.D.*
Gary Kimmel, Ph.D.*
Allan Marcus, Ph.D.*
Kevin Mayer*
Robert Park
John M. Rogers, Ph.D.
Ralph Smialowicz, Ph.D.*
Glenn Suter, Ph.D.*
Edward Urbansky, Ph.D.*
Douglas C. Wolf, DVM, Ph.D.

"The Right Stuff"

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Toxicological Review and Risk Characterization
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March 5 & 6, 2002 Sacramento, CA

2002 Overview

- Background
  - 1999 External peer review recommendations
  - Conceptual Mode-of-Action Model
  - New studies and results
- Assessment approach highlights
  - Human health
  - Ecotoxicological
- Public comment issues and clarifications
- Summary

1999 External Peer Review

- Basis of health assessment
  - Thyroid histopathology in PND5 rat pups
  - Histopathology used as biomarker for adverse hormonal changes *in utero*
- Screening level ecotoxicological assessment
  - Agreed with characterization
  - Identified additional data gaps
- Scientific expert peer findings
  - Concurred with conceptual model and nonlinear approach
  - Supportive of concern for neurodevelopmental
  - Provided recommendations

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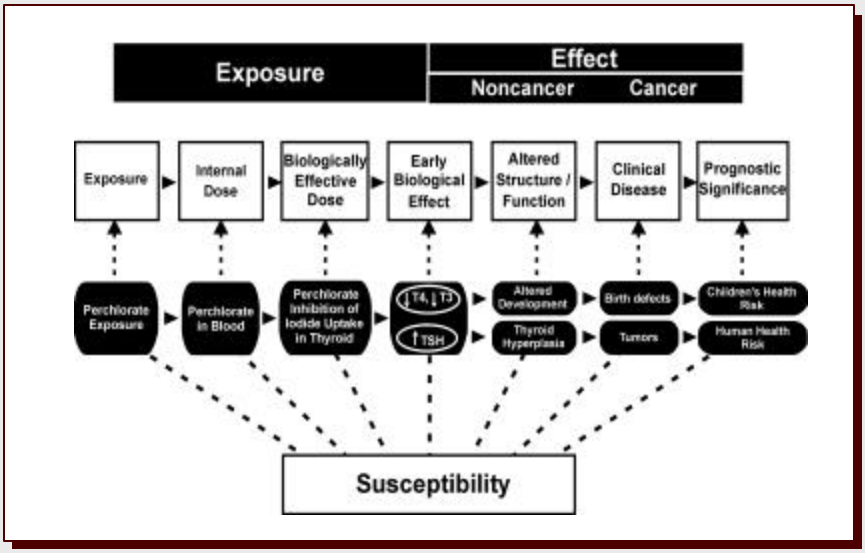
Proposed Mode-of-Action Model for Health Risk Assessment of Perchlorate



1999 Peer Review Recommendations

- Evaluate variability in RIA kits across laboratories
- Pathology Working Group of thyroid histopathology
- Additional brain morphometry if material available
- Developmental study in rats
- Repeat motor activity study in rats
- Repeat and additional immunotoxicity studies in mice
- Pharmacokinetic information in humans and rats
- Alternative statistical analyses for hormone data
- Chronic ecotoxicological studies
- Additional ecotoxicological receptors
- Data on transport and transformation

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Recommendation Responses

- EPA and NIEHS performed PWG on thyroids
- Protocols reviewed by EPA
  - Not all protocols were EPA guideline studies
  - Not all suggestions from EPA taken
  - EPA testing guideline studies or modifications
    - Developmental study in rats
    - Brain morphometry and motor activity in rats
- Performed and reported by DOD, PSG, or their contractors
- EPA and NIEHS independent analysis
  - Additional statistics as deemed appropriate
  - Peer-review of those data not submitted to scientific literature

New Studies: Humans

- Observational (ecological) epidemiological studies
  - Not part of testing strategy
  - Limited exposure measures, demographic data, population size and outcome measures
  - Lack of control for confounding
- Clinical studies
  - 3 different laboratories
    - Greer et al. (2000)
    - Lawrence et al. (2000) and (2001)
    - Unpublished data from Drs. H. Leitolf and G. Brabant
  - EPA had limited input on one (Greer et al. 2000) at outset; designed with intent to provide pharmacokinetic information and not to designate effect levels
  - Those that underwent QA/QC used to develop human PBPK model and others to support validation

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US EPA ORD NCEA

EPA Interim Human Study Policy

- Federal agencies adhere to "common rule" guidance that includes informed consent
- Agency has long-standing concern for "third-party" human data
  - Intentional dosing with toxicant to determine effect levels
  - IRB information often unavailable
  - Issue is how to ensure adherence on *post hoc* basis
- Moratorium issued on December 14, 2001 re: use of this type of data **in the future** until the NAS determines criteria for acceptability
  - Human studies were considered and shortcomings noted in assessment
    - Studies not used to determine hazard based on human NOAEL
    - "What if" calculation was provided
  - Human data were used to support the AFRL PBPK model

New Studies: Laboratory Animals

- Pathology Working Group (PWG) of previous data
  - Thyroids: colloid depletion, hypertrophy, hyperplasia
  - Brains: Insufficient materials
- AFRL interlaboratory study of RIA kits to measure hormones evaluated across 3 laboratories
- Argus 1999 two-generation reproductive study in rats
- Argus 2000 developmental study in rats
- USN (Bekkedal et al., 2000) motor activity study in rats

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New Studies: Laboratory Animals

- "Effects study" protocol in rats (Argus, 2001)
  - Hormones and thyroid histopathology in pups and dams
  - Brain morphometry
- Immunotoxicity study in mice
  - Repeat macrophage phagocytosis
  - Sheep red blood cell (SRBC) assay of humoral immunity
  - Contact hypersensitivity

New Studies: Ecotoxicology & Exposure

- Acute (EA Engineering, 1999)
  - *Selanstrum caprinconutum* 96-hr
- Subchronic ecoxoticity (Block Env. Svcs., 1998)
  - Pimephales promelas 7-day
- Chronic ecotoxicity (Block Env. Svcs., Inc., 1998; EA Engineering, 2000)
  - *Pimephales promelas* 35-day Early Life Stage
  - *Hyalella azteca* definitive 28-day study
  - *Ceridaphnia dubia* 6-day
- FETAX studies
  - Dumont and Bantle, 1998
  - Goleman et al., 2002

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New Studies: Ecotoxicology & Exposure

- Six site-specific occurrence & biotransport studies (Parsons Engineering, 2001)
  - Site media
  - Various ecological receptors @ each site
- Phytotransformation and plant uptake studies
  - Nzengung et al., 1999; Nzengung and Wang, 2000
  - Susarla et al., 1999; 2000
- Occurrence & biotranport studies
  - US Army Corps of Engineers (Condike, 2001): fish
  - Smith et al., (2001): water, sediments, vegetation, fish, mice
- Indirect exposure characterizations
  - EPA Fertilizer study with The Fertilizer Institute (US EPA, 2001a,b)
  - Wolfe et al., 1999; Ellington et al., 2001; Urbansky, 2000

Designation of Effect Levels

- Thyroid histopathology
  - Benchmark response @ 10%
  - BMDL used as NOAEL surrogate in RfD derivation
- Thyroid hormones
  - Response level @ 10%
  - Analysis of Variance (ANOVA)
- Brain morphometry
  - Repeated measures issue — T-tests inappropriate
  - Profile analysis
    - Mulitvariate analysis of variance
    - Vector does not require expectation on magnitude or direction
  - Issues on sectioning addressed with restricted analyses
    - PND21
    - Sidedness, normalization, region and level

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Designation of Effect Levels

- Motor activity data from Argus 1998 DNT and USN
  - Bayesian hierarchical analysis with linear mixed-effects regression
  - Individual studies and data combined
  - Results indicate effects @ 1 mg/kg-day
- Thyroid tumors in Argus 1999 two-gen study
  - 3 tumors in 2 animals @ 19 weeks in F1 adults
  - Compared to incidence of all thyroid tumors in NTP archives for SD-rats @ 2-year bioassay terminal sacrifice
  - Bayesian analysis
  - Results indicate concern for *in utero* programming
    - Latency
    - Incidence

Point of Departure

- Key event defined as an empirically observable precursor step that is a necessary element or marker for mode of action
- Identified as iodide uptake inhibition @ the Na^{+}-$Iodide^{-}$ Symporter (NIS)
  - Reinforced by repeat studies showing neurodevelopmental effects
  - Precursor for thyroid hormone perturbations
  - Allows harmonization in approach to address neurodevelopmental and neoplastic sequelae
- Weight of evidence for 0.01 mg/kg-day LOAEL
  - Thyroid and pituitary hormones
    - Dams on GD21
    - Pups on GD21, PND4 and PND9
    - 14-days and 90-day for T4 and TSH
  - Thyroid histopathology
    - Pups on PND4 in 1998 and 2001 and weanlings in 1999
  - Brain morphometry in pups on PND21

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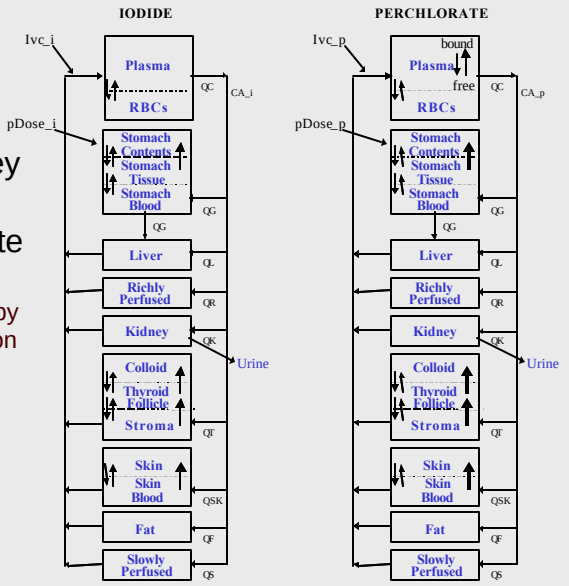
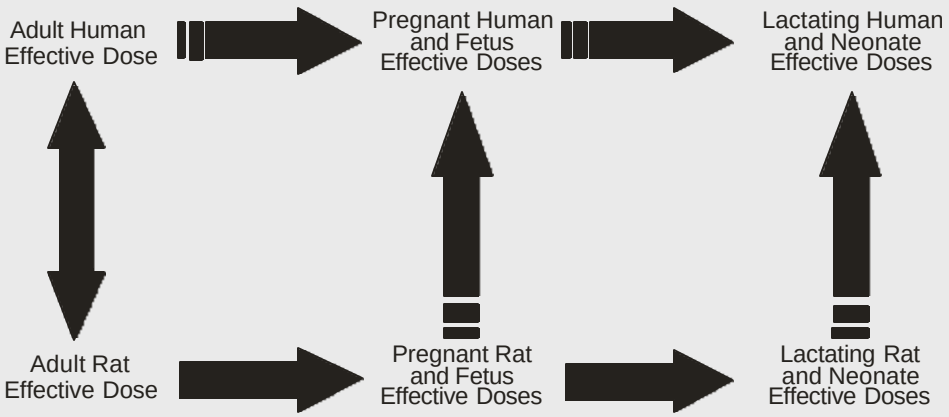
AFRL Dosimetry Model Structures

- 4 Model Structures
  - Adult male rat
  - Adult human
  - Pregnant rat & fetus
  - Lactating rat & fetus
- Compartments for key tissues
- Iodide and perchlorate disposition
  - Active uptake described by Michaelis-Menten saturation
  - Permeability areas cross products and partitions
  - Passive diffusion
  - Plasma binding
  - Urinary elimination
- Growth



Parallelogram Extrapolation



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US EPA ORD NCEA

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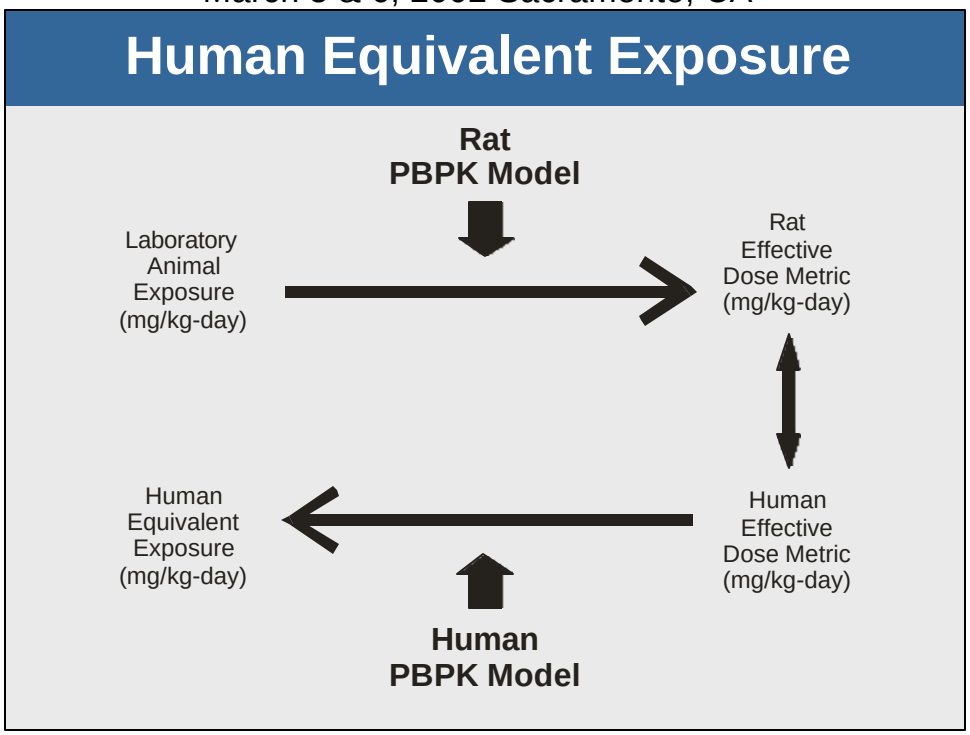

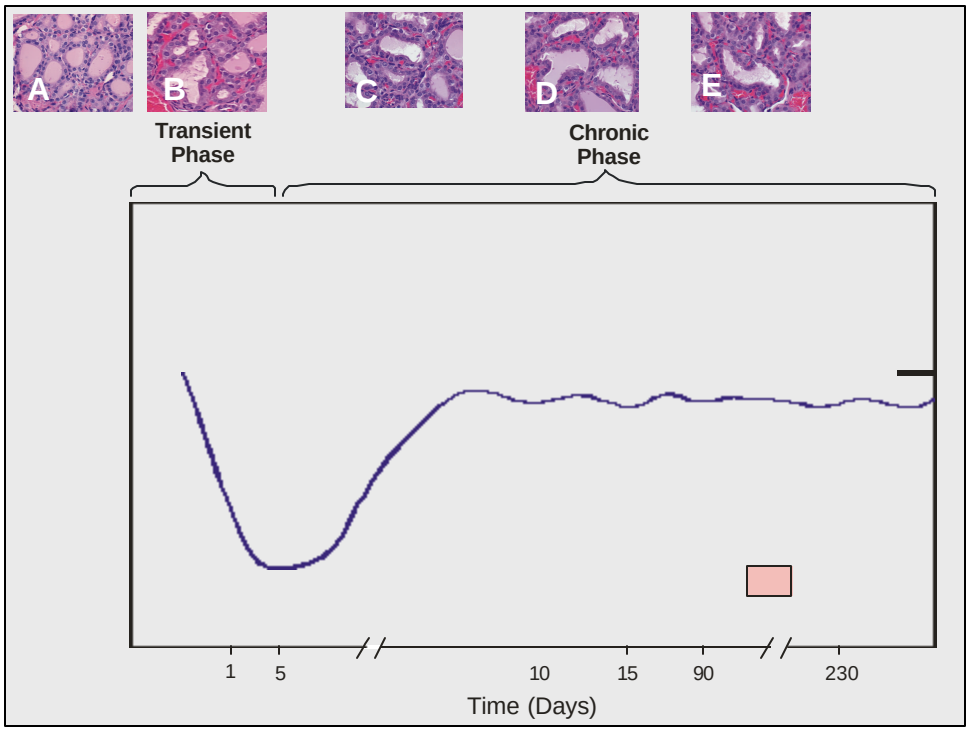

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Choice of Dose Metric

- Internal perchlorate concentration as metric associated with key event of iodide inhibition
  - iv data in rats ("acute")
  - Drinking water in humans
- Area Under the Curve in (AUCB) blood versus peak
  - Good correlation with iodide inhibition
  - Average of serum and thyroid
- EPA agreed with DOD re: uncertainty in and lack of validation of thyroid parameters notably in fetus and neonates for iodide inhibition description
- HEE based on maternal AUC in blood at GD21

Uncertainty Factors

- Composite factor of 300 parceled into components
  - Intrahuman: 3
    - Pharmacokinetic variability
    - Not representative of sensitive populations
  - Interspecies: None
    - PBPK dosimetry model for extrapolation
  - LOAEL to NOAEL: 10
    - Hormones (slope), thyroid histopathology and brain morphometry
    - Interdependence with lack of interspecies and choice of dose metric
  - Subchronic to chronic duration: 3
    - Lack of "womb to tomb" design and *in utero* programming concern — recalibration of feedback system
    - Interdependence with intrahuman factor
  - Database Insufficiencies: 3
    - Concern for immunotoxicity reinforced

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Operational Derivation

RfD (mg/kg-day) = 0.01 x 0.85 ✹ 300 = 0.00003

Where:

- 0.01 is the point of departure
- 0.85 adjusts to perchlorate anion alone
- 300 is the composite uncertainty factor

Comparative Risk Derivations

- "What if" calculation based on human data
  - 0.007 mg/kg-day
  - Uncertainty factor of 100 parceled as:
    - Intrahuman variability: 3
    - LOAEL to NOAEL: 3
    - Subchronic to chronic duration: 3
    - Database insufficiency: 3
  - Result is 0.00007 mg/kg-day
- If a larger UF was applied for intrahuman variability then resultant estimate would be essentially equivalent to that proposed

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Comparative Risk Derivations

- Derivation based on tumor precursor lesions
  - Colloid depletion, hypertrophy and hyperplasia all observed @ > 0.3 mg/kg-day
  - BMDL estimates of 0.9, 0.15 and 0.0004 mg/kg-day
  - HEE estimates of 0.45 and 0.02 for colloid depletion and hypertrophy
  - Uncertainty factor of 100 parceled as:
    - Intrahuman variability: 3
    - LOAEL to NOAEL: 3
    - Subchronic to chronic duration: 3
    - Database insufficiency: 3
  - Result is in range of 0.005 to 0.0002 mg/kg-day
  - A larger UF for intrahuman variability would result in 0.002 to 0.00007 mg/kg-day

Hypothetical RfD Conversion

- Critical to distinguish the RfD from any guidance value that may result
- Conversion to drinking water equivalent level (DWEL) in ug/L (ppb):
  - Adjustment by 70 kg and 2 l
  - DWEL = 1 ug/l (ppb)
- Derivation of maximum contaminant level goal (MCLG) typically involves the use of a relative source contribution (RSC) factor to account for non-water sources of exposures
  - Range of 0.2 to 0.8
  - Default @ 0.2 when data are inadequate to determine
  - Result would be MCLG between 0.2 to 0.8 ug/l (ppb)

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Ecotoxicological & Exposure

- Screening-level and not definitive
- Exposure issues:
  - Accumulation in terrestrial and aquatic plants
  - Fate in irrigated soils
  - Potential for dietary toxicity to vertebrate herbivores point to need for lower limits of detection in plant and animal tissues
- Effects need determination:
  - Exposure on aquatic plants and noncrustacean invertebrates
  - Dietary exposures in birds and in herbivorous or litter-feeding invertebrates
  - Dietary and cutaneous exposure for adult amphibians and aquatic reptiles

Summary: Unique Attributes

- Pro-active partnership to develop data
- Model motivated by mode of action
- Harmonized approach to noncancer and cancer toxicity based on key event
- Human and ecosystem health
- Comprehensive characterization — integrated approach challenging
  - Analytical
  - Occurrence / exposure / transformation & transport
  - Assessment approaches
  - Treatment technology

Annie M. Jarabek
US EPA ORD NCEA

Appendix J

Post-Meeting Comments Submitted by Peer Reviewers

Note: After the peer review meeting, ERG distributed to the peer reviewers copies of additional public comments received before the submissions deadline (April 5, 2002). The peer reviewers were given the opportunity to prepare post-meeting comments based on the information in these public comments or on any other topics they chose to address. This appendix contains all post-meeting comments that peer reviewers submitted to ERG. ERG modified the format of these comments, but did not alter the content.

Post-Meeting Comments Submitted by Dr. Thomas Collins:

Note: During the peer review meeting (see Section 4.2), Dr. Thomas Collins expressed concern about apparent dose-dependent decreases in sperm density and daily sperm production levels observed in a laboratory animal study (Argus 1999). After the meeting, Dr. Collins sent technical questions, through ERG, to the study's authors regarding the sperm analyses. Following are Dr. Collins' questions, responses to these questions from one of the study's authors (Dr. Raymond York), and Dr. Collins' post-meeting comments regarding these responses.

Question #1 (regarding sperm evaluation):

Dr. Collins' question:

"Does the percent motility presented in the report refer to 'progressive motility' or to 'motility'? If this value represents 'progressive motility,' how was 'progressive motility' defined using the Hamilton-Thorne Sperm Analysis System?"

Dr. York's written response:

"The value represents motile sperm versus nonmotile sperm. We have never been able to validate 'progressive motility' for GLP studies. We have been able to validate curve linear velocity, average path velocity but not smooth line (straight line) velocity or beat-cross frequency which are needed in the calculations."

Dr. Collins' comment on the response:

"Acceptable."

Question #2 (regarding tissue evaluation):

Dr. Collins' question:

"What embedding material was utilized for the testicular tissue? Paraffin? Methacrylate? How were the samples stained? PAS? H and E?"

Dr. York's written response:

"The protocol-specified tissues were routinely processed, embedded in paraffin, sectioned and stained with hematoxylin and eosin for microscopic evaluation. The copy of page 817 from the final report is attached." (See page 817 of Argus 1999 for attached material.)

Dr. Collins' comment on the response:

"Argus laboratories indicated that testicular tissues were routinely processed, embedded in paraffin and stained with hematoxylin and eosin (H and E). Testicular tissues have traditionally been immersion-fixed with formalin and embedded in paraffin for

histological observation, however it is generally accepted that the use of this fixative induces many artifacts and that subtle changes in testicular histology may be missed or not observed. Many testing guidelines (FDA, EPA, OECD, and ICH) suggest using Bouin's fixative or another suitable fixative to preserve testicular tissues. It is surprising that Argus laboratories continued to use formaldehyde as the fixative of choice for the fixation of testicular tissues. Because the testicular tissues were not fixed utilizing appropriate fixatives, histopathological data should be considered questionable with respect to more subtle changes which may have occurred in the seminiferous epithelium but not with respect to more gross histopathological changes."

Question #3 (regarding sperm density):

Dr. Collins' question:

"To what do the authors attribute this reduction in cauda epididymal sperm density in 30-mg/kg/day-dose group of the F1 generation?"

Dr. York's written response:

"Cauda epididymal sperm density was 1543.6 ± 520.8 for the control male rats in the F1 generation and 1372.6 ± 444.6 for the male rats in the 30 mg/kg/day exposure group. The authors attribute the reduction in cauda epididymal sperm density in 30 mg/kg/day dose group to chance. The data for this parameter had overlapping standard deviations indicating a common dispersion of data points and there was no statistical difference when an ANOVA, the workhorse of toxicology, was applied. The ANOVA is very robust for moderate departures from equality of variances when the sample sizes are approximately equal."

Dr. Collins' comment on the response:

"Acceptable."

Question #4 (regarding sperm density):

Dr. Collins' question:

"Why is the sperm density for the P and F1 controls so dramatically different?"

Dr. York's written response:

"The raw data for this study was re-reviewed. The age, body weight and caudal weight for the male rats of both generations were approximately the same. The settings on the Hamilton-Thorne Sperm Analysis System were the same for both generations. We believe the difference is a matter of a slight difference in technique between two technicians. Technician #1 analyzed all 119 samples of the P generation epididymal sperm concentration by himself while Technician #2 ran most of the F1 generation (98 samples), with Technician #1 running some samples (18 samples). Technician #1's counts

were lower than Technician #2, on average, which we discovered and discussed at the time. What we determined then was that Technician #1 handled the homogenates differently than Technician #2 did when he made the stained sample from the homogenate. Technician #2 would invert several times and then vortex, pipetting the sample of while the homogenate was still spinning from vortexing, keeping the cells in suspension and, hopefully, evenly distributed. Technician #1 would vortex, then when the sample stopped spinning he would invert several times, and draw the sample. When Technician #1 used Technician #2's ordering of steps, he also achieved higher counts. It may seem odd, but sometimes a small difference in ordering of steps will produce a significant difference in the results. Technician #1's range of values overlapped Technician #2's range, but Technician #2 was higher overall than Technician #2, so Technician #2 would fall on the high end of the bell curve and Technician #1 would fall on the low end. This did not show up on the spermatid counts for this study because Technician #1 and Technician #2 split the analyses more evenly, each doing about half of the samples."

"I have also attached the Testing Facility's historical control for the Hamilton-Thorne Sperm Analysis System. It includes the type of study, date report finalized and covers 1314 rats from 51 studies conducted 1998 through 2002. The Sponsor's protocol number has been removed except for this study. The average sperm density is 1099.9 with a range of 730.7 to 1563.9 so the sperm density values for both generations for this study fall within the historical control range but towards the two tails. By reviewing the historical control file, it can be noted that 5 multigenerational studies have been completed since the two-generation ammonium perchlorate study (Code 353A and B; protocol 1416-001). The codes and sperm density values for the P and F1 generation control rats for these studies are 489A (1255.0) and B (940.2); 513A (1046.8) and B (1010.8); 522A (1044.8) and B (1061.0;) and 570A (962.7) and B (1194.3)."

Dr. Collins' comment on the response:

"The authors indicated that the differences between the sperm density counts in the P and F1 generation were attributed to technicians using different techniques to prepare samples for analysis with the Hamilton-Thorne Sperm Analysis System. This would suggest that one or both of the technicians did not follow the Standard Operating Procedures for the preparation of sperm samples for analysis by CASA. This could compromise the results because not all samples were handled in a similar manner. Although this explains the different counts obtained between the two generations, it still does not explain the non-significant dose-related decrease in sperm density and daily sperm production observed in the F1 generation. It seems unlikely that a dose related decrease in sperm density would occur if two different technicians using different techniques for sample preparation randomly assayed the samples. Although an examination of the historical control data indicated that the counts obtained from the animals in the 30-mg/kg/day-dose group were within the range of historical control values, the dose related decrease in sperm numbers observed in the F1 generation is still puzzling. Because two different methods were utilized for the determination of testicular spermatid densities and because of the

unexplained dose-related decrease in spermatid density in the F1 generation, spermatid density data should be considered questionable but should not be discounted with respect to the accuracy of the spermatid counts."

Post-Meeting Comments Submitted by Dr. David Hoel:

Point of departure based on human data:

The Greer et al. 2002 study provides the best data for NOAEL estimation of iodine uptake. If the data for the original study are combined with the data from the subsequent 0.007 mg/kg dose group one finds a good fit using percentage uptake at 24 hours and 14 days versus the log of administered dose. One individual is a clear outlier (mj in the 0.007 mg/kg) and is eliminated from the analysis. The regression yields Percentage uptake = 0.230 –0.88*log(dose). The data is well described by this expression which predicts a no-effect level (as opposed to a NOAEL) of 0.005 mg/kg. Using the lower limit of the 95% confidence interval the no-effect level becomes 0.0025 mg/kg. If one includes a covariate for the background uptake level one obtains the expression: Percentage uptake = 0.401 – 0.18 background – 0.85 log (dose). For a background level of 0.1 mg/kg the no-effect level value is 0.008 mg/kg and 0.0045 mg/kg for a background level of 0.2 mg/kg. Since the concern is with those with a lower background level using a value of 0.005 is conservative. Comparing this data with that of the other clinical study by Lawrence one finds that the Lawrence study estimates a somewhat higher value for the no-effect level. We therefore conclude that a very conservative human point of departure is 0.0025 mg/kg/day. Considering the large amount of human data which is generally negative it is reasonable therefore to use an uncertainty factor of 3 for intra-human variability. This results in a reference dose of 0.0008 mg/kg. If a more conservative uncertainty factor of 10 is desired then one has a reference dose of 0.00025 mg/kg. I would, however, use the value 0.0008 mg/kg/day as an RfD since conservatism has already been incorporated into the calculation prior to applying the 3x uncertainty factor. Further it is not clear that a small reduction in iodine uptake indicates any adverse health effect.

Human Clinical Studies:

Concerns are raised about the fact that the clinical studies were carried out on healthy adults. This concern, if valid, should also then be expressed with the toxicological studies since the rodents are presumably also healthy and genetically even more homogeneous than the humans.

Peer Review:

One minor comment is on the idea that EPA considers a thesis as a peer reviewed paper. The problems with this view are as follows:

1) Often only the student and the advisor are expert in the topic and not the other committee members.

2) Often little attention is given by other committee members to the research work especially for a MS thesis which is not necessarily required to be publishable.

3) In journal reviews the editor seeks out the most knowledgeable and anonymous reviewers which one does not have with a graduate advisory committee.

4) After publication problems and errors with a paper can be brought to everyone's attention through "letters to the editor."

5) I know of theses whose results have been rejected for publication in the scientific literature.

Post-Meeting Comments Submitted by Dr. Merle Paule:

In the absence of convincing changes in brain morphometry, the point of departure using only changes in thyroid hormone, TSH and thyroid histology becomes hard to defend. In the absence of another study to replicate, yet again, the morphometric findings, it should be more expeditious to have the morphometrics analyzed again by a blinded expert. While several peer review members indicated that they were comfortable with the interpretation of the morphometric data proffered by the EPA staff, it was clear that several others felt they would never be able to trust the data from the Argus 2001 study.

It is also critical, that in any attempts at replicating rodent studies (and likely those of other species), time of year (season) needs to be taken into consideration and controlled. The effects of chemicals in animals can vary tremendously from winter to summer, even when such animals are housed inside, with no known exposure to natural light, etc. It is my opinion, that the difficulty in (or inability to) replicate rodent studies may in some cases relate to seasonal confounds.

In general discussion with other reviewers who also were asked to assess the Bekkedal motor activity study; the consensus was that the data did in fact indicate a signal (effect) of perchlorate exposure: Specifically, the 18 day old males and the 22 day old females showed perchlorate effects when the Bayesian analysis was employed. Similarly, Bayesian analysis of the behavioral data from an earlier Argus study also showed effects, albeit in 14 day old subjects. The absence of an effect in the 14-day-old animals in the Bekkedal study was not considered problematic because of issues surrounding the ability to replicate findings in rodents.

If follow-on studies are undertaken, it is clear that much more sophisticated behavioral analyses need to be employed to explore the potential of perchlorate-induced functional deficits. These could include but not be limited to: studies on classical conditioning (thought to depend, at least in part, on cerebellar function); learning tasks (hippocampal function); and attention tasks (frontal cortical function).

Several observers at the Workshop brought up the issue of potentially confounding effects of diet: soy-based products or others may contain compounds with the ability to interact with and influence thyroid hormones or TSH. This possibility needs to be explored and it needs to be determined whether the diets used in the earlier studies might have affected the outcome of those studies. If so, studies with other diets that do not have the ability to influence the system would need to be conducted.

In general, this reviewer feels that the Agency did an exceptional job of providing reasonable analyses and interpretations of the data and in defending the Uncertainty Factors proposed. After discussion at the workshop, the consensus of the panel was clearly leaning toward eliminating the UF of 3 for database insufficiency, based on the lack of concern expressed by the immunologist on the panel for the likelihood that perchlorate may have adverse effects on immune system function. Those arguments were persuasive, but, of course, if one were to poll

other immunologists, one might get different perspectives. I would not, however, feel uncomfortable about dropping the UF of 3 for database insufficiency.

The issue of the inverted U-shaped dose-response curve for endpoints used to support the point of departure need to be clearly telegraphed to the non-science stakeholders. This is a confusing issue, but such non-linear relationships are not uncommon. Thus, while I am not skeptical of the existence of such a relationship in the perchlorate matter, a clear explanation of such will be necessary.

Post-Meeting Comments Submitted by Dr. Thomas Zoeller:

1. Borak, J. and Russi, M. Comments on: Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization (External Review Draft January 16, 2002)

The executive summary identifies 3 "value judgements" made by the EPA in its document which these authors find problematic:

1. Exclusion of the clinical studies as "principal studies" for use in the risk assessment.
2. Use of the animal studies despite the almost certain confounding variable of the diet containing soy protein.
3. Characterization of the Schwartz epidemiological study by the EPA as a "strong" study.

CRITIQUE:

1. Neither the EPA nor a regulated industry should define the ethics of identifying a LOAEL/NOAEL for compounds in humans. This is an issue that is reasonably considered by a national body such as the NAS, which the EPA has contacted.

2. The authors are unreasonably secure in their argument that the ARGUS studies were confounded by isoflavones (e.g., genestein) in the diet. Although this is an important hypothesis that should be formally evaluated, the diet used by ARGUS is a very common one in rodent studies. Therefore, if there were the kind of confound the authors propose, and as described by Ikeda *et al.* (1), it would be very obvious in the literature considering the values for TSH reported in the *Carcinogenesis* paper (1). This report indicates that animals on the soy-enriched diet exhibited TSH levels of about 125 ng/ml. This is greater than 10-fold higher than what is considered to be elevated TSH levels in rats, produced by the well-known goitrogenic agents methimazole (MMI) and propylthiouracil. In fact, I have recently completed a study in my lab combining MMI and 0.5% perchlorate and still observed TSH levels in the 10-20 ng/ml range, unlike the astronomical values of Ikeda *et al.* Thus, although it is important to consider this kind of potential interaction, it is highly unlikely that it has any bearing on the ARGUS studies. The TSH levels reported in the ARGUS studies were not outside those observed in the thyroid literature, and certainly were not in any way similar to that reported by Ikeda *et al.*

3. Characterization of the Schwartz Thesis. These are potentially valid comments, though I don't believe I have an original copy of the Schwartz thesis and therefore cannot comment. See the public comments by Schwartz.

2. Bruce, G. and Pleus, R.C. Summary of the Expert Review of the ARGUS, 2001 ("Effects Study") Evaluation of Perchlorate Effects on Brain Morphometry in Neonatal Rats.

Conclusions regarding the adequacy of the methodology in the ARGUS 2001 Effects study.

a. *Use of coronal sections.* There is no doubt that coronal sections were not optimal for all the brain areas measured. However, for others, it was. Finally, linear measures were not the best choice of endpoint – though there are no valid and validated endpoints in the developing brain for thyroid toxicity.

b. *Use of single width measures*. The corpus callosum measurements are clearly not reliable in coronal plane.

c. *Lack of evaluation of post-puberty animals.* In both humans and animals, perinatal thyroid insufficiency produces a lag in myelination that "catches up" later in development. However, both humans impacted by postnatal hypothyroidism and rats experimentally manipulated to model this deficiency, exhibit permanent neurological deficits despite the "catch up" in certain measures. Thus, the requirement for persistence of an anatomical anomaly is not valid.

d. *Lack of demonstrated association between changes in linear dimensions of brain structures and the presumed mode of action of perchlorate (hypothyroidism).* It is true that there is no information linking incremental deficits in thyroid hormone levels with linear brain measurement. In fact, there is no information linking incremental deficits in thyroid hormone levels with anything. Did the experts propose a series of endpoints that have been validated for toxicological studies such as ARGUS 2001?

e. *Lack of a positive control*. This is simply wrong. We know enough about perchlorate mechanism of action that using a drug like methimazole or PTU which acts in a fundamentally different way with different pharmacokinetics compared to perchlorate is a weak and illogical design. Rather, using T_4 to ameliorate the effects of perchlorate, restoring levels to those within a physiological range, would be better.

f. *A clear dose-response relationship is not apparent.* It is not logical to assume, *a priori*, that linear measures of brain structures will exhibit a clear dose-response with perchlorate. The control of size of brain structures is not well understood. The role of thyroid hormone in this process is not well understood. The relationship between thyroid hormone activation of receptors and down-stream events that may play a role in controlling the size of specific brain structures is also not well understood. What possible basis would experts have to conclude that this should be a requirement for a clear dose-response relationship between perchlorate and size of individual brain structures as measured by a single linear measurement?

g. *Hypothyroidism was not induced.* (see discussion of #7)

3. Goodman-1. Letter to EHP editor.

No comment

4. The DoD Perchlorate Working Group. "Comments on the U.S. Environmental Protection Agency's Draft Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization (NCEA-1-0503, 16 January 2002)

Several points are made and expanded in the text:

1. Issue of using clinical studies (see above)
2. Argue that the use of brain morphometry and thyroid hormone levels are problematic because of the inconsistencies. These inconsistencies were well-recognized by the peer-review group and it is clear that there are problems. However, these data are endpoints with the most important implications and need to be emphasized in the EPA analysis.
3. Argues that "The screening benchmark for herbivores should be derived using toxicity values associated with endpoints known to be ecologically relevant (development, reproduction)." I fully disagree with this statement because, in my opinion, it is based more on the common practice of using reproductive endpoints in toxicity studies because those endpoints are better developed, not because they are more important or valid. Because reproduction can occur even in cretins – the most severe form of developmental defect due to thyroid hormone insufficiency – I believe it is not wise to use reproductive indices alone in evaluating the toxicity of a compound like perchlorate which affects the thyroid.

5. Schwartz, H. public comments, "<u>Thyroid Hormone Effects on the Developing Brain: Critical Review…".</u>

The Executive summary concludes that, "For all these reasons, we must conclude that the reported results are artifacts of methodology and are of no value in evaluating the possible effects of perchlorate in the rat. Dr. Schwartz presents a clear set of arguments to support this conclusion. However, many of these arguments are weak, if not incorrect, and this reduces the strength of the conclusion. These arguments are as follows.

A. The concept of a "critical period" of thyroid hormone action on the rat brain, as defined by Dr. Schwartz, is incorrect. Dr. Schwartz defines the critical period of thyroid hormone action in rodents (rat) as the early postnatal period, and that this period is absolute. Recent studies show that maternal thyroid status of the dam can influence gene expression (2-4), behavior (5), hearing (6), and migration of cortical neuroblasts (7). The Dowling studies also show clearly that changes in maternal T_4 *within the physiological range*, can affect the expression of known thyroid hormone-responsive genes in the fetal brain <u>before the onset of fetal thyroid function.</u> Thus, it is incorrect to assert that thyroid hormone of maternal origin does not play an important role in fetal brain development, even before the onset of fetal thyroid function. The important conclusion from these studies is that it is more appropriate to think of "critical" periods of thyroid hormone action in specific developmental contexts. For example, Schwartz

demonstrated that manipulating maternal thyroid status late in gestation did not influence MBP gene expression in the late-gestation fetus (8). This is undoubtedly a valid, reliable, and important observation as it relates to the control of myelination in the cerebellum. However, it is inappropriate to consider MBP regulation by thyroid hormone to be a surrogate marker of thyroid hormone effects on the entire brain at all times.

B. Dr. Schwartz describes the effects of hypothyroidism on rat development as it has been amply shown throughout many years and studies, and correctly observes the lack of these effects in the Argus studies. Specifically, lowered growth rate of the dams, her fetuses and her pups. However, it cannot be overemphasized that the thyroid literature is characterized by the use of high doses of potent goitrogens and the production of severe hypothyroidism. In no case were animals exposed to multiple doses of these goitrogens with the goal of identifying a NOAEL/LOAEL of thyroid hormone. Although pharmacodynamic studies exist for some goitrogens (9), they have not been performed to look at effects on the brain. Therefore, it is not valid to directly compare the dose-response studies of perchlorate in the Argus studies with this body of literature. Having said that, Dr. Schwartz is absolutely correct in stating that the Argus studies used endpoints of perchlorate toxicity that were completely devoid of any known relationship to thyroid hormone. Moreover, this point was made clearly in the first Peer Review meeting and this fact alone weakens the interpretation of the Argus studies. However, it must also be recognized that even known markers of thyroid hormone action on the developing rat brain have not been validated for the kind of toxicological screen used in the Argus studies.

C. The concept that we can surmise that changes in circulating levels of thyroid hormone did not produce adverse effects in the brain would obviate all empirical measures of neurotoxicity of chemicals that reduce circulating levels of thyroid hormone. For example, we could simply surmise that a threshold of thyroid hormone levels exist, above which no adverse effects can be assumed and below which adverse effects can be assumed. The fact is that no experimental studies to date have attempted to identify a NOEL for thyroid hormone deficits on specific measures of thyroid hormone action in the developing brain that control important developmental events. Therefore, the conclusion of Dr. Schwartz is unwarranted. Moreover, the assumption that we can predict or calculate the thyroid hormone decrement in maternal serum required to observe an adverse effect on the brain is based on estimates of receptor occupancy taken from whole brains and pooled. This is valid if and only if the brain is a homogeneous aggregation of cells with respect to thyroid hormone, which is clearly not the case.

D. The effect of perchlorate on linear measures of the brain are not validated measures of thyrotoxic endpoints, as Dr. Schwartz points out. However, the use of a goitrogen as a positive control would be less valuable than demonstrating that the effect(s) of perchlorate on brain development could be ameliorated with exogenous T_4. Clearly, with all the research focused on perchlorate, there is little doubt about its mechanism of action.

6. Wahlsten, D. Summary and Re-Analysis of Data: Brain morphometry results from a perchlorate toxicity study (Primedica 2001).

Dr. Wahlsten reanalyzed the data from the Argus 2001 "Effects" study and found that there was a small but statistically significant increase in the thickness of three brain regions, including the frontal cortex, the parietal area and the striatal area. This is a reasonable analysis of the data acquired in the ARGUS study. The critical element of Dr. Wahlsten's comment is that the analysis should consider the size of the effect as well as their statistical significance. Dr. Wahlsten presents a very strong argument that there are in fact treatment effects. However, he argues that these effects are not biologically significant because they are not large. Considering that the measures under consideration are simple linear measurements of brain regions, it is impressive that any effects were observed. Moreover, it is important to recognize that any observed effects must necessarily be related to reductions in thyroid hormone. If there is an effect on the size of specific brain regions, then it is not unreasonable to infer that there are potentially a number of effects that do not contribute to size, such as neurochemical effects.

7. Bruce, G., Peterson, M., Lincoln, D.R., and Pleus, R.C. Review and assessment of TSH and thyroid hormones during pregnancy in the rat and human and comparison to hormone values in the 2001 Effects Study.

Bruce *et al.* propose that gestational TSH and thyroid hormone levels in normal (control) rats can be compiled across many publications to generate a "reference" range to which the values in the Argus 2001 "Effects Study" can be compared. Bruce *et al.* state that, "Reported mean TSH concentrations for pregnant control rats late in gestation (gestational day [GD] 19 to 22), range from 0.43 to 469 ng/mL." Using this reference range, it is found that the TSH levels are not outside this "normal" range following perchlorate exposure in the ARGUS 2001 study. It is my understanding that the authors are suggesting that this range should reflect a "reference" for pregnant rats. There are several reasons this is not possible. First, the laboratories from which the data were obtained to determine this reference range were not using pools to calibrate their assays across laboratories. It is likely that they were not all using the same reference preparation – they may not have even been using purified TSH for the reference standard and for labeling from the same source. Clearly, a TSH level of 469 ng/mL is not believable, so the authors do not seem to be using critical judgement in evaluating the literature. For these reasons, it is absolutely essential that studies such as ARGUS 2001 include control groups and that the control groups are used as the reference to which all other measures are compared. This kind of comparison will also take into consideration the potential confounding variables that the authors suggest are problematic. Using appropriate controls, and avoiding systematic errors such as sampling different groups at different times of day or on different days, is simply basic scientific methodology. The same logic holds for all the other hormones measured in ARGUS 2001.

The authors of this comment appear to misunderstand the concept of hypothyroidism. Clinically, a diagnosis of hypothyroidism requires low T_4 and high TSH (outside the reference range) and the simultaneous presentation of some of the symptoms of hypothyroidism.

Translating this definition to rats is somewhat difficult because there is no such reference range for thyroid hormones (see above) and because usually clinical observations are not sophisticated as it applies to rats. Accordingly, the term hypothyroidism applied to rats usually refers to the most severe situation where rats are treated with a potent goitrogen (methimazole or propylthiouracil), exhibit undetectable T_4 and TSH levels above 10 ng/mL. Clearly, perchlorate did not induce hypothyroidism (as the term is used in the literature) in rats in the ARGUS 2001 Effects Study. However, in rats as in humans, subtle hypothyroxinemia can produce adverse effects especially if it occurs during development. Thus, the issue is not whether the animals exhibited hypothyroidism, it is whether the hypothyroxinemia produced by perchlorate produced adverse effects.

Factors contributing to variability in measured TSH and thyroid hormone levels. Hormone levels within the hypothalamic-pituitary-thyroid axis all vary significantly over the 24 hour day. This is not technically a circadian rhythm (which would imply that it persists in the absence of light/dark cycles. However, ensuring that blood is collected at the same time of day, staggered across treatments, is clearly the best way to perform the experiment. It is highly unlikely that temperature changes would have in any way affected the ARGUS studies. I studied cold exposure in rats for a number of years (10-16). Small changes in temperature for short duration do not affect hormone levels. Moreover, cold exposure produces effects in the afternoon, not in the morning (13). Considering this, temperature changes associated with routine maintenance of the animals is not likely to affect the results in any way.

8. Soldin, O.P., Nandedkar, K.N., Japal, K.M., Stein, M., Mosee, S., Magrab, P., Lai, S., Lamm, S.H. Newborn thyroxine levels and childhood ADHD.

This paper is based on the assumption that neonatal T_4 is a valid biomarker of pre-natal thyroid status. This is clearly false. There is a great deal of evidence demonstrating that prenatal thyroid status can be variable without being indicated by the point-estimate of thyroid status at the time of birth.

9. Lockheed Martin Corp. Comments on U.S. EPA's perchlorate environmental contamination: toxicological review and risk characterization.

1. EPA's External Peer Review lacked a single medical expert on the subject of the thyroid. The authors argue that clinical endocrinology is central to the issue under debate, and therefore, the peer review committee should have included clinical endocrinologists specializing in thyroid endocrinology. Drs. Greer and Braverman were highlighted for their expertise. Clearly, Drs. Greer and Braverman are truly distinguished physician scientists. However, neither of these clinicians studied the role of thyroid hormone in development. Thus, it would have been a valid argument to include clinicians experienced in clinical thyroidology who study the effects of maternal or postnatal hypothyroxinemia on neurological function.

2. EPA's External Peer Review panel included interested participants. The authors argue that Dr. Zoeller's inclusion on the peer review raises at least the appearance of partiality because he was a returning member of the '99 peer review panel and because he was cited by the Environmental Working Group in their "Report" on perchlorate. First, I would like to point out that my criticisms of the animal studies provided to the '99 peer review were very similar to those being articulated by the authors reviewed above in the present document. Specifically, the use of linear measures in brain morphometry was poorly supported. Why use the statistical approach being used? Etc. However, I was critical because I thought that these criticisms would lead to a change in the approach that could have prevented some of the problems associated with those studies as has been amply debated. Thus, it seems disingenuous to argue that my comments were biased in the '99 peer review meeting but other's are not biased now.

Second, it is reasonable to wonder about the integrity of a scientist cited in the EWG report, which is accurately portrayed as "long on hyperbole and short on science". However, I have made a great number of public comments before and since that time that can and should be held up to scrutiny as to my propriety, bias, and partiality.

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Appendix K

Index of Written Materials Submitted by Observers at the Peer Review Meeting

During the observer comment period, several observers distributed written materials to the peer reviewers for their consideration. Some of these materials were copies of the comments spoken at the meeting (i.e., those documented in Appendix H), but others were supplemental information not covered during the observer comments. Following is an index of the written materials that observers submitted during the observer comment period:

Name of Submitter	Title of Written Materials	Number of Pages
Mike Dourson	Key Findings	5
Richard Pleus, Ph.D.	Were the Highest Doses of Perchlorate Sufficient to Cause Adverse Effects in Dams and Their Offspring?	1
Gay Goodman, Ph.D., D.A.B.T.	Thyroid Function, Perchlorate Mode of Action, and Interspecies Differences: Presentation to the Peer-Reviewers of the EPA/NCEA External Review Draft of January 16, 2002	6
Monte A. Greer, M.D.	Why It is Essential to Use Human Dose-Response Data to Evaluate the Human Health Risk of Perchlorate in Drinking Water: Presentation to the Peer-Reviewers of the EPA/NCEA External Review Draft of January 16, 2002	6
Dan Guth, Ph.D.	Oral comment to perchlorate peer review workshop	7
Douglas Walsten, Ph.D.	Re-analyses of data on rat brain morphometry and motor activity	1
La Donna White, M.D.	Testimony for U.S. EPA Peer Review Workshop on Perchlorate draft reference dose	2
Jonathan Borak, M.D.	Figure 3 from Ikeda et al.: *Carcinogenesis* 21:707–713, 2000	2
David R. Mattie, Ph.D., D.A.B.T.	Transport of perchlorate into thyroid cells	2
John Gibson	Comments by John Gibson - CEO - American Pacific Corporation	2
DoD Perchlorate Working Group	Comments on the U.S. Environmental Protection Agency's Draft Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization	49
No name on document	DoD Perchlorate Talking Points	6