

COMMENTS of PROFESSOR GAGIK MELIKYAN

pertaining to Proposed Amendments to Title 27, California Code of Regulations Sections 25821(a) and (c)

***Level of Exposure to Chemicals Causing Reproductive Toxicity:
Calculating the “Level in Question” for a Food Product and the Intake by the
Average Consumer of a Product***

Part I. Introduction

1. I am providing these comments as an expert in the fields of organic, organometallic, medicinal, enzymatic, computational, hormonal, and food chemistries, cancer drug development, endocrine disruptors, environmental toxicants, consumer product chemistry, human health risk and exposure assessment, as well as in application of these subjects to litigation cases related to California's Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65") and pertinent state and federal regulations.

2. I am a Professor of Chemistry in the Department of Chemistry and Biochemistry at California State University Northridge (CSUN) with 45 years of the professional experience conducting cutting-edge interdisciplinary research. My original contribution to science has culminated in numerous research publications (88), including nine invited reviews and book chapters, as well as presentations (131) at national and international conferences, scientific gatherings, and public forums (*Exhibit A*). The said contribution was recognized by awarding me the prestigious *Outstanding Faculty Award* and *Jerome Richfield Scholar Award*, the highest distinctions given by the university in recognition of excellence in faculty research. I am also a recipient of *The Kennedy Center Stephen Sondheim Inspirational Teacher Award* (Washington, D.C.). The work emanated from my laboratory was widely covered in print media, and through radio and TV outlets (*Exhibit A*).

3. I am the author of the award-winning book titled *"Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics"* (2009, 368pp; www.imaginethetruth.com). In laymen terms, the book explains why chemical compounds in household items, foods, supplements, cosmetics, plasticware, jewelry, and other consumer products can cause irreparable damage to human health by being carcinogens, mutagens, teratogens, reproductive toxins, or endocrine disruptors. I am also an editor of on-line educational program (newsletters, youtube videos) that bring the latest news on consumer products and related health issues to the general public.

4. Over the last decade, as an expert and consultant, I have provided litigation support to consumer protection groups, served as an expert witness in toxic consumer product torts (cosmetics; foods; electronics; petrochemicals), supported non-profit organizations in the "failure to warn" litigations and the state actions initiated under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), petitioned government agencies on listed carcinogens and reproductive toxins, provided consulting services to cosmetic industry on cosmetic formulations, rendered consulting services on environmental pollution related to irresponsible mining practices and environmental product liability cases, provided technical guidance on sampling protocols for environmental pollutants, prepared expert declarations, provided trial depositions, developed wiping protocol for phthalates, conducted human exposure and health risk analysis, evaluated interactions between commercial products and the consumer population, and quantified the exposures to listed chemicals from materials in dispute according to NSRL and MADL standards.

5. I have a detailed knowledge of California's Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65") [1] through my involvement with multiple projects as a consultant and an expert. I have an in-depth understanding of the Proposition 65 mission, societal ramifications, public health implications, major provisions, warning requirements to potential exposure to listed chemicals, basis for listing chemicals as carcinogens or reproductive toxins, warning obligations for businesses, and legal consequences for failure

to warn. Since 2009, I have been providing scientific backing to a number of litigations involving consumer products, such as foods, cosmetics, household items, and technical gadgets. The types of activities included evaluation of rebuttal files submitted by businesses in response to civil lawsuits alleging violations of the Proposition 65 requirement to warn, assessment of exposure to listed chemicals from consumer products in dispute, providing depositions, and testifying as a court expert witness.

6. I have carefully reviewed the proposed amendments to Title 27, California Code of Regulations Sections 25821(a) and (c) titled *“Level of Exposure to Chemicals Causing Reproductive Toxicity: Calculating the “Level in Question” for a Food Product and the Intake by the Average Consumer of a Product,”* and an “Initial Statement of Reasons,” as well as the proposed regulatory text. Overall, I have a broad and extensive personal knowledge of the matters related to the averaging of human exposure to reproductive toxicants, determining the “levels in question,” and alternative algorithms for conducting said calculations.

PART II. Comments on OEHHA Proposed Amendments to Title 27, California Code of Regulations Sections 25821(a) and (c) *“Level of Exposure to Chemicals Causing Reproductive Toxicity: Calculating the “Level in Question” for a Food Product and the Intake by the Average Consumer of a Product”*

7. The current Proposition 65 description of averaging the exposure to reproductive toxicants in food products is confusing, and allows for misinterpretations. It fails to provide sufficiently specific instructions as to how the “level in question” must be calculated, thus creating disputes between enforcers and the regulated community.

8. The averaging algorithms for exposure to reproductive toxicants that have been used by the defendants and their experts in Prop65 litigation cases, include the multiple modes of averaging that cumulatively result in the grossly diminished assessment of the exposure in question. Examples of these averaging modes that either have been used, or potentially can

be used, are as follows: averaging the concentration of the toxicant in food products for different batches, different lots, different manufacturers, different producers, different sellers, or different manufacturing facilities. The general outcome of these practices is the decrease in actual exposure thus misleading the general population with respect to the consequences of consuming adulterated food products, creating a false sense of safety with respect to the products sold in the State of California, and potentially becoming a public health hazard of enormous proportions. For example, one defendant sells one lot or batch of a food product in Northern California with levels of a listed chemical high enough to exceed the NSRL and/or MADL which would have required a warning. The same defendant sells another lot or batch of that food product in Southern California that contains no listed chemical, and thus would not require a warning. But when the test data of these two lots or batches are averaged together, the resulting “level in question” does not exceed the NSRL or MADL. Thus, the amendments to the regulations should be specific enough to prevent this type of situation.

9. The proposed amendment to section 25281(a) that pertains to calculating the “level of question” is long overdue, and I enthusiastically support the OEHHA-initiated new regulation. It explicitly states that arbitrary averaging of the level of toxicants will no longer be allowed, thus removing the existing deficiency, and eliminating the averaging concept as a tool for potential downward manipulations. At the same time, the current wording in section (a) is not sufficiently exhaustive, still leaving space for misinterpretations. *The wording introduced must exclude the averaging in general and clearly state that for food items that can be found in the American marketplace, the “level in question” must be such that the respective MADL or NSRL thresholds are not exceeded.*

10. In addition to OEHHA’s Regulations indicating that for certain reproductive toxicants “The reasonably anticipated rate of exposure shall be based on the pattern and duration of exposure that is relevant to the reproductive effect which provided the basis for the determination that a chemical is known to the state to cause reproductive toxicity. (For

example, an exposure of short duration is appropriate for a teratogenic chemical...)” (27 CCR § 25821(b)), there is a separate reason why exposures to listed chemicals like heavy metals should not be averaged over time. This alternative reason derives from the significant disparity in daily retention for Prop65 listed chemicals, both organic and inorganic (entries 12 and 13 below).

11. For some chemicals like heavy metals, their daily retention rate is much higher than that of other chemicals, and complete removal can be possible not in 24 hours, but in weeks, months, or even years. The urgency for addressing this aspect of toxicity for calculating exposure to toxic chemicals like heavy metals, and their compounds, is substantiated by Prop65 statistics. Since the inception of this legislation, the Attorney General’s office received a total of 11,572 60-day notices related to six listed metals (lead, 8688; cadmium, 939; arsenic, 714; chromium, 545; mercury, 357; nickel, 329). The sheer volume of said submissions coming from consumer protection groups and private enforcers reveals the widespread presence of these toxic metals in food products, and also underlines how critical it is for public health to correctly calculate exposure in question.

12. Lead Exposure Based on Hypothetical Scenario: To demonstrate how the calculation mode could alter the numerical data that pertains to alleged exposure to toxicants, let us use lead as an example, and assume that 10mg of toxicant are introduced on day 1 and daily excretion is equal to 5%. On day 1, the exposure is equal to 10mg/day (introductory dose). On day 2, 95% of the initial amount will still be inside the body (10mg x 0.95 = 9.5mg), and throughout day 2, the body will be exposed not to 10mg, but 9.5mg/day. Assuming that the remaining amount of lead will be secreted (5%) every day until day 10, average exposure can be calculated as the following:

$$\begin{array}{l} \text{average} \\ \text{exposure} \\ \text{per day} \end{array} = \frac{(10 + 9.5 + 9.0 + 8.6 + 8.1 + 7.7 + 7.4 + 7.0 + 6.7 + 6.3)\text{mg}}{10\text{days}} = 8 \text{ mg/day}$$

The hypothetical scenario thus presented demonstrates why simple averaging (10mg:10days=1mg/day) is not scientifically correct, and how much lower exposure data would be received if the actual retention of the toxins in the human body is not taken into consideration (8mg/day vs 1mg/day).

13. Lead Exposure Based on Experimental Data: In this section, not hypothetical, but published data on lead retention are used to estimate the actual exposure of the human body to this toxicant. Experimental studies on lead excretion and retention were carried out with stable lead isotope tracers with the concentration of toxicant being determined in bodily fluids, in particular in blood [2; Exhibit B]. The tests were carried out with healthy adults which were given the lead compound for periods of up to 124 days, with ingestion being discontinued on days 52, 82, 104, and 124, and blood being analyzed on the indicated day (total of 128 analyses). By using those analytical data, lead retention rates were calculated for select days by using alternative algorithms (consecutive days; alternating reference days; Figure 1). In particular, for a one month period, retention of lead was established as follows: day 1, 97%; day 2, 92%; day 3, 91%; day 4, 87%; day 5, 85%; day 6, 85%; day 7, 80%; day 8, 75%; day 9, 71%; day 10, 76%; day 11, 74%; day 12, 67%; day 14, 66%; day 30, 33%.

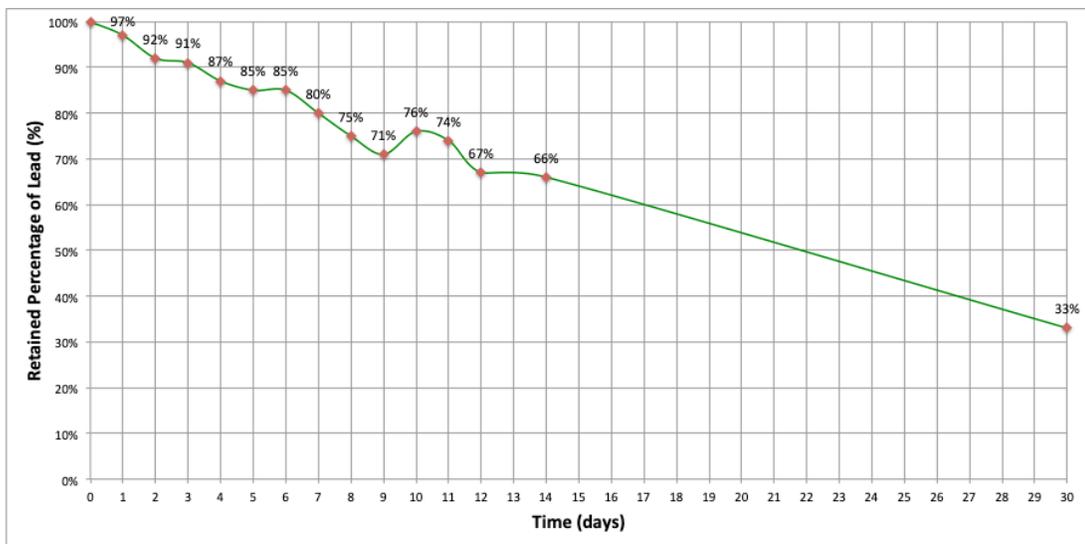


Figure 1. Retention rate of lead over 30 days.

66%; and day 30, 33%. These data represent experimental proof that most of the initial dose of lead introduced on day 1, was still present on day 2 (97%), indicating a very high retention rate, and correspondingly, a very slow excretion rate. The one-day retention of 97% of lead is equivalent to injecting a new dose of lead on day 2, which is equal to 97% of the initial dose introduced on day 1. Analogously, the three-day retention of 91% of lead is equivalent to injecting a new dose of lead on day 3 equal to 91% of the initial dose introduced on day 1 (Figure 1). The high retention of lead is further highlighted when one-week intervals are used over a 4-week period (1 week, 80%; 2 weeks, 66%; 4 weeks, 34%; Figure 2).

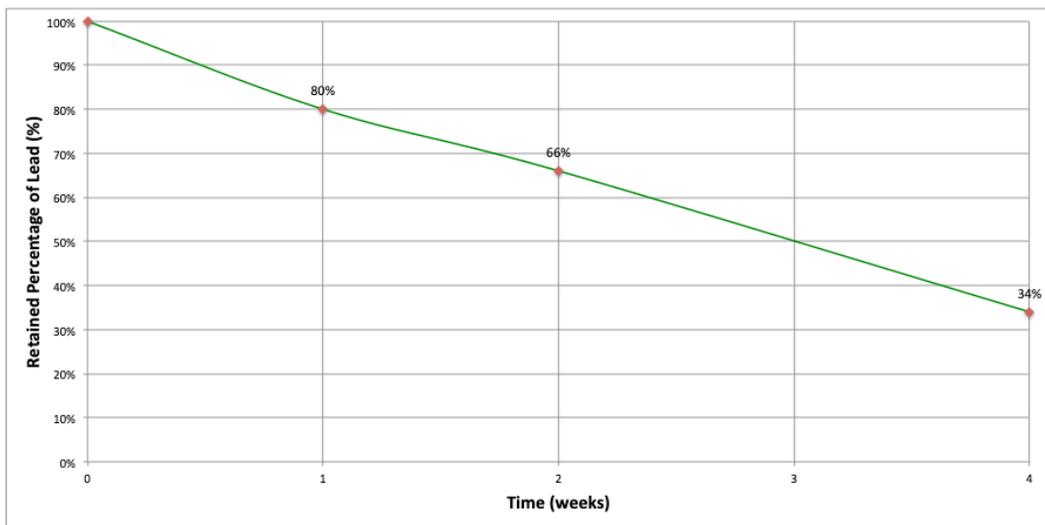


Figure 2. Retention rate of lead over four weeks with a one-week increment.

14. I enthusiastically support the proposed amendment that pertains to calculating intake **as an arithmetic, not geometric, mean** (*Section 2: ... This rate of intake or exposure is calculated as the arithmetic mean of the rate of intake or exposure for users of the product.*). Over the last decade, on multiple occasions I have been encountering relentless attempts by the experts representing defendant businesses to use geometric means instead of arithmetic ones. In communications related to Prop65 enforcement, I have pointed out – repeatedly – that geometric mean values were systematically lower than the arithmetic mean values, underestimate the human exposure to a given toxicant, and most importantly, their use was

not scientifically justified. The former was designed to deal with subjects when each item has multiple properties that in turn have substantially different numeric ranges. Food product analyses do not fall into this category because analytical data for toxicants such as lead or cadmium, in most cases fall within a narrow range, and usually, there are no outliers that could be different from the main set of parameters by orders of magnitude (much higher or much lower than most of the values recorded). Although there is a legal case(s) wherein the geometric mean values were accepted by the court, the said precedence does not add any credence to it from the scientific point of view.

Part III. Recommendations

15. The proposed regulatory amendments will remove ambiguity regarding the averaging algorithms and calculation modes, thus providing enforcers and businesses with scientifically sound mechanisms of assessing the exposure to reproductive toxicants *before* the product is introduced into the marketplace, and triggers legal actions on behalf of consumer protection groups and private enforcers.

16. Some modifications are warranted to further clarify the listing and explicitly define what the averaging means, what kind of averaging is scientifically acceptable, and how the averaging paradigms must be adjusted for different classes of reproductive toxicants based on their actual retention by the human bodies.

I recommend that the Proposition 65 proposed amendments to the *“Level of Exposure to Chemicals Causing Reproductive Toxicity: Calculating the “Level in Question” for a Food Product and the Intake by the Average Consumer of a Product”* be modified as follows:

OEHHA’s proposed regulatory text

27 CCR § 25821 § 25821. Level of Exposure to Chemicals Causing Reproductive Toxicity

(a) For purposes of the Act, “level in question” means the chemical concentration of a listed chemical for the exposure in question. The exposure in question includes the exposure for which the person in the course of doing business is responsible, and does not include exposure to a listed chemical from any other source or product. For purposes of this section, where a business presents evidence for the “level in question” of a listed chemical in a food product based on the average of multiple samples of that food, the level in question may not be calculated by averaging the concentration of the chemical in food products from different manufacturers or producers, or that were manufactured in different manufacturing facilities from the product at issue.

Suggested regulatory text amendment that pertains to averaging

For purposes of this section, where a business presents evidence for the “level in question” of a listed chemical in a food product based on the average of multiple samples of that food, the level in question may not be calculated by averaging the concentration of the chemical in food products from different batches, lots, producers, sellers, or manufacturing facilities, as well as the combinations thereof. Instead, averaging in general should not be applied, and for every food item, the “level in question” must be such that the respective MADL/NSRL thresholds are not exceeded.

Suggested ADDITIONAL regulatory text that accurately calculates the reasonably anticipated rate of exposure

For consumer products, which are not consumed or used on a daily basis, but once every several days ($EO < 1$), no simple averaging of the exposure over time should apply. If the toxicant, either organic or inorganic, is not completely removed in 24 hours, or less, then the level in question must be calculated by taking into consideration an actual retention of a given toxicant by the human body and a daily accumulation of the toxicant exerting the cumulative toxic effect.

OEHHA's proposed regulatory text

(2) For exposures to consumer products, the level of exposure shall be calculated using the reasonably anticipated rate of intake or exposure for average users of the consumer product, and not on a per capita basis for the general population. This rate of intake or exposure is calculated as the arithmetic mean of the rate of intake or exposure for users of the product ...

Suggested regulatory text amendment

Fully supported, no suggestions.

OEHHA's proposed regulatory text

(2) ... The rate of intake or exposure shall be based on data for use of a general category or categories of consumer products, such as the United States Department of Agriculture Home Economic Research Report, Foods Commonly Eaten by Individuals: Amount Per Day and Per Eating Occasion, where such data are available.

Suggested regulatory text amendment

The rate of intake or exposure shall be based on data for use of a general category or categories of consumer products, such as the United States Department of Agriculture Home Economic Research Report, Foods Commonly Eaten by Individuals: Amount Per Day and Per Eating Occasion. Nothing in this section prevents the use of alternative databases or sources of information whenever deemed appropriate or scientifically justified.

PART IV.

17. I reserve the right to modify my opinions as new information is discovered or brought to my attention.

18. I am available for taking part in public hearings, or expert panel discussions, as well as for presenting findings to the Carcinogen Identification Committee of OEHHA's Science Advisory Board.

Dated 12 01 18

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book website: <http://imaginethetruth.com>

research website: <http://www.csun.edu/science-mathematics/chemistry-biochemistry/gagik-melikyan>

References

- [1] Health and Safety Code section 25249.5 et seq., The Safe Drinking Water and Toxic Enforcement Act of 1986, commonly known as “Proposition 65”.
- [2] Rabinowitz, M. B.; Wetherill, G. W.; Kopple, J. D. Kinetic Analysis of Lead Metabolism in Healthy Humans. *The Journal of Clinical Investigation* **1976**, *58*, 260-270.

EXHIBIT A

CURRICULUM VITAE

MELIKYAN, Gagik G., Professor of Chemistry, Department of Chemistry and Biochemistry, California State University Northridge (CSUN), Northridge, CA; tel. off. 818-677-2565; email: gagik.melikyan@csun.edu; research website: www.csun.edu/science-mathematics/chemistry-biochemistry/gagik-melikyan; book websites: www.csun.edu/gmelikyan and www.imaginethetruth.com.

RESEARCH INTERESTS

Radical reactions of transition metal-complexed unsaturated systems; synthetic methodologies in organic and organometallic chemistry; novel therapeutic agents for a breast cancer treatment; enzymatic chemistry; cancer drug development; aromatase metabolism; hormonal chemistry; food chemistry; antioxidants; supplements; cosmetics; environmental chemistry; consumer product chemistry; environmental laws.

CONSULTING AND EXPERT SERVICES

2006-to-date provided litigation support to consumer protection groups; served as an expert witness in toxic consumer product torts (cosmetics; foods; electronics; petrochemicals); supported non-profit organizations in the “failure to warn” litigations and the state actions initiated under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65); petitioned government agencies on listed carcinogens and reproductive toxins; provided consulting services to cosmetic industry on cosmetic formulations; rendered consulting services on environmental pollution related to mining practices and environmental product liability cases; provided technical guidance on sampling protocols for environmental pollutants; prepared expert declarations; provided trial depositions; developed wiping protocol for phthalates; conducted human exposure and health risk analysis; evaluated interactions between the commercial products and consumer population; quantified the exposures to listed chemicals from materials in dispute according to NSRL and MADL standards.

PUBLICATIONS & BOOKS & PATENTS & PRESENTATIONS & PETITIONS

87 papers in peer-reviewed journals, including
9 reviews/book chapters;
1 book;
3 patents;
132 presentations including:
national, regional, and international conferences – 65 (7 - invited);

- invited talks at academic institutions – 18;
- public hearings on carcinogens and reproductive toxicants at the state and federal agencies – 1;
- expert depositions and trial testimonies on carcinogens and reproductive toxicants on behalf of the consumer protection groups – 4;
- invited public presentations – 30;
- radio interviews – 9;
- TV interviews – 5;
- 10 expert declarations on carcinogens and reproductive toxicants on behalf of the consumer protection groups;
- 6 chairing sessions at ACS national and regional conferences;
- 1 petitioning state and federal agencies to protect American public from carcinogens and reproductive toxicants.

BOOK *Guilty Until Proven Innocent: Antioxidants, Foods, Supplements and Cosmetics*. Delta 2010, 368pp.

SCIENTIFIC CITATION SCORES (as of 05.09.14)

- 874 sum of the times cited;
- 626 sum of times cited without self-citations;
- 17 h-index.

PUBLIC OUTREACH: EXPLAINING CHEMISTRY TO THE GENERAL PUBLIC

50,095 number of views of the health-related youtube videos.

PROFESSIONAL EXPERIENCE

- 1978-1990 Institute of Organic Chemistry, National Academy of Sciences, Yerevan, Armenia: Principal Researcher (1990); Senior Research Fellow (1983-1990); Junior Research Fellow (1978-1983); Research Group Leader (1978-1990);
- 1990-1992 Alexander von Humboldt Fellow, Institute of Organic Chemistry, University Erlangen-Nurnberg, Erlangen, Germany;
- 1993-1995 Adjunct Professor of Chemistry, Department of Chemistry&Biochemistry, University of Oklahoma, OK;
- 1995-1998 Assistant Professor of Chemistry, Department of Chemistry, CSUN, Northridge, CA;
- 1998-2003 Associate Professor of Chemistry, Department of Chemistry, CSUN, Northridge, CA;
- 2003-to-date Professor of Chemistry, Department of Chemistry&Biochemistry, CSUN, Northridge, CA.

NEW REACTIONS DISCOVERED

- 1984 palladium-induced, one-step transformation of 5-alkyn-4-olids to 4E-alkenoic acids;

- 1990 oxidative methylene-extrusion reaction converting 2H-pyrans into furan derivatives;
- 1997 conversion of propargyl alcohols into cyclic and acyclic 1,5-alkadiynes mediated by heteroatom-containing organic molecules;
- 2003 spontaneous generation and coupling of Co-complexed propargyl systems.

NEW CONCEPTS and TERMS INTRODUCED INTO SCIENCE

- 2006 “unorthodox organometallic radical chemistry”;
- 2013 “sequestered” organometallic radicals;
- 2015 “chiralization by metal complexation”;
- 2015 “caged triple bond”;
- 2018 “background/threshold steric factor.”

INVITED PRESENTATIONS AT CONFERENCES (from a total of 7)

- 1999 35th ACS Western Regional Meeting, 1999 Pacific Conference, Ontario CA;
- 2000 American-German-French Symposium “Carbon-Rich Organometallics”, Erlangen, Germany;
- 2002 National Foundation on Science & Advanced Technologies (NFSAT)-Civilian Research & Development Foundation (CRDF, Washington) 5th Anniversary Conference, Yerevan, Armenia;
- 2008 International Organometallics Conference 2008, ZING Conferences, Cancun, Mexico;
- 2009 General Assembly, National Academy of Sciences, Yerevan, Armenia.

CHAIRING SESSIONS AT ACS CONFERENCES

- 1998 “Organometallic Synthesis,” 34th ACS Western Regional Meeting, 1998 Pacific Conference, San-Francisco, CA;
- 2011 “New Reactions and Methodology,” 241st ACS National Meeting, Anaheim, CA;
- 2012 “Metal-Mediated Reactions and Syntheses,” 243st ACS National Meeting, San Diego, CA;
- 2013 “Metal-Mediated Reactions and Syntheses,” 245st ACS National Meeting, New Orleans, GA;
- 2014 “Asymmetric Reactions and Syntheses,” 246st ACS National Meeting, San Francisco, CA;
- 2015 “New Reactions and Methodology,” 250st ACS National Meeting, Boston, MA.

INVITED PRESENTATIONS AT ACADEMIC INSTITUTIONS (total of 18)

UC San Diego, CA (1997); CSU Los Angeles, CA (1998); USC, Los Angeles, CA (1999); UC Riverside, CA (1996); University of Oklahoma, Norman, OK (1993); University of Erlangen-Nurnberg, Germany (1992); University of Hamburg, Germany (1991); University of Hannover, Germany (1991); Institute of Organic

Chemistry, NAS, Yerevan, Armenia (1991); Department of Natural Sciences, NAS, Yerevan, Armenia (1998, 2009); University of Pierre and Marie Curie, Paris, France (2001); CSU Long Beach, CA (2009); California State University Northridge, Northridge, CA (2014); University of Oklahoma, Norman, OK (2014); California State University Northridge, Northridge, CA (2015); University of Southern California (USC), Los Angeles, CA (2017).

DISTINCTIONS & RECOGNITIONS

- 2002 *Polished Apple Award*, University Ambassadors, CSUN, Northridge, CA;
- 2008 *Outstanding Faculty Award*, CSUN, Northridge, CA;
- 2008 *Foreign Member*, National Academy of Sciences, Yerevan, Armenia;
- 2010 *Jerome Richfield Research Scholar Award*, CSUN, Northridge, CA;
- 2015 *The Kennedy Center Stephen Sondheim Inspirational Teacher Award*, Washington, D.C.

LITERARY AWARDS

- 2011 *Finalist* in the "Science" category, The USA "Best Books 2011" Awards competition sponsored by the USA Book News;
- 2012 *Second Place Award* in the "Science" category, 2012 International Book Awards competition sponsored by JPX Media.

AWARDS & HONORS

- 1970-1973 "Best Student of the Department of Chemistry", Department of Chemistry, Yerevan State University, Yerevan, Armenia;
- 1987 Deutscher Akademischer Austauschdienst (DAAD), Germany;
- 1990 Alexander von Humboldt Fellowship, Germany;
- 1997 Collaborative Research Award, Civilian Research and Development Foundation (CRDF);
- 1998 Hewlett Packard Corporation;
- 1998 Judge Julian Beck Foundation;
- 2001 NATO, Physical and Engineering Science and Technology;
- 2002 American Chemical Society, Petroleum Research Fund;
- 2006 America's Registry of Outstanding Professionals 2005-2006;
- 2006 Who's Who in Sciences Higher Education (WWSHE);
- 2007,2011 National Science Foundation (NSF), Research at Undergraduate Institutions (RUI).

EDUCATION

- 1973 B.S. in Chemistry, Yerevan State University, Yerevan;
- 1977 Ph.D. in Organic Chemistry, Institute of Elementorganic Compounds, National Academy of Sciences, Moscow;
- 1990 D.Sc. (Doctor of Sciences) in Organic/Organometallic Chemistry, Institute of Organic Chemistry, National Academy of Sciences, Yerevan;

1990-1992 Alexander von Humboldt Fellow in Organic/Organometallic Chemistry, Institute of Organic Chemistry, University Erlangen-Nurnberg, Erlangen, Germany.

TEACHING RESPONSIBILITIES

Courses taught at CSUN since 1995 (12WTU/semester):

CHEM103 General Chemistry I;
CHEM235 Introductory Organic Chemistry (for non-Science majors);
CHEM331 Organic Chemistry I (for Chemistry majors);
CHEM332 Organic Chemistry II (for Chemistry majors);
CHEM331L Organic Chemistry I Laboratory course;
CHEM332L Organic Chemistry II Laboratory course;
CHEM333 Principles of Organic Chemistry I (for Science majors);
CHEM334 Principles of Organic Chemistry II (for Science majors);
CHEM333D Principles of Organic Chemistry I Discussion;
CHEM334D Principles of Organic Chemistry II Discussion;
CHEM333L Principles of Organic Chemistry I Laboratory course;
CHEM334L Principles of Organic Chemistry II Laboratory course;
CHEM595F Organometallic Chemistry (for graduate students).

INDIVIDUAL STUDENT TRAINING & MENTORING

1984-1992 4 graduate students awarded Ph.D. degrees;
1999-2018 12 graduate students awarded *Master of Science* degrees;
1996-2018 graduate (up to 3/semester) and undergraduate (up to 6/semester) students enrolled in CHEM696, CHEM495, and CHEM499 courses (total number of research students – 102, including 91 undergraduate students; total of 546 student-semesters including 376 undergraduate student-semesters);
1997-2018 122 student presentations (including 73 - by undergraduate students) at the departmental, school, university, state and national levels, including the ACS National and Regional Meetings, Southern California Conferences on Undergraduate Research, National Conferences on Undergraduate Research (NCUR), CSUN Student Research Symposia, CSU-Wide Students' Research Symposia, Sigma Xi Competitions, American Association for the Advancement of Science (AAAS) Annual Meetings;
1996-2018 53 student awards (including 36 by undergraduate students), such as Donald Bianchi Research Awards, Best Presentation, 1st, 2nd and 3rd Place Awards at Sigma Xi Competitions (CSUN, 1996, 1997, 1998, 1999, 2003, 2005, 2006, 2007, 2009, 2013, 2015); First Place Awards at CSUN Student Research Symposia (CSUN, 1996, 1997, 2004, 2005, 2007, 2010, 2013); Second Place Award at CSUN Student Research Symposia (CSUN, 2002; 2006, 2010, 2013, 2014, 2018); Second Place Award at CSU Student Research Competition (CSU Chico, 1998); Second Place Award at CSU Student Research Competition (CSU Hayward, 2008), Nathan O. Freedman Memorial Award (CSUN, 2010); Outstanding Junior Award (CSUN,

1998); Hypercube Scholar Award (CSUN, 1999); Organic Chemistry Award (CSUN, 2000, 2012); Outstanding Graduate Student Teaching Award (CSUN, 2005, 2007, 2009); Graduate Fellow Award for Outstanding Research Promise in Science and Mathematics (CSUN, 2009); First Place Award, Award of Excellence, AAAS Pacific (San Francisco, 2010), Outstanding Freshman Chemistry Award (CSUN, 2011); Analytical Chemistry Award (CSUN, 2011); Henry Klostergard Award for Outstanding Graduating Chemistry Major (CSUN, 2012); Outstanding Graduating Senior Award (2014); 2014 Wolfson Award (2014); Outstanding Oral Presentation Award, ACS Southern California Undergraduate Research Conference (SCURC, 2015, 2017); Leslie and Terry Cutler Scholarship Award (2015); 2016 National Science Foundation (NSF) Graduate Research Fellowship Program (GRFP) Fellowship (2016); 2018 Dr. Vanessa Bustamante Greek Leadership Scholarship Award (2018); Third Place Award, American Association for the Advancement of Science (AAAS) Annual Meeting, Pacific Division, Pomona, CA (2018).

1996-2018

31 student proposals (funded – 26; submitted by undergraduate students – 16, funded - 15), University Corporation, CSUN; Associated Students, CSUN.

CURRICULUM DEVELOPMENT / PROFESSIONAL SERVICES

- I. Revised the curriculum of Organic Chemistry laboratory for chemistry majors (CHEM331L/332L) bringing up the level of instruction to that in research laboratory;
- II. Introduced high-resolution chromatographic methods and state-of-the-art experiments into Organic Chemistry curriculum;
- III. Initiated and ran new seminar series for undergraduate and graduate students “Students’ Research Seminar”;
- IV. Evaluator, Single-subject credential evaluation of science teacher;
- V. Acted as a member, and chaired, the Curriculum Committee, College of Science and Mathematics, CSUN;
- VI. Coordinated Organic Chemistry laboratory courses (CHEM235/333/ 334);
- VII. Acted as a library liaison for Department of Chemistry&Biochemistry;
- VIII. Continuously upgraded undergraduate Organic Chemistry lecture courses;
- IX. Faculty Hearing Panel, CSUN;
- X. Post Promotion Increase (PPI) Committee, Department of Chemistry&Biochemistry, CSUN;
- XI. Judge, 12th Annual Sigma Xi Student Research Symposium, CSUN;
- XII. Member, Part-time faculty personnel committee, Department

- of Chemistry and Biochemistry, CSUN;
 XIII. Member, Department Chair Search and Screen Committee,
 Department of Chemistry and Biochemistry, CSUN;
 XIV. Member, Post-tenure faculty evaluation committee,
 Department of Chemistry and Biochemistry, CSUN;
 XV. Organic Chemistry Faculty Hiring Committee, Department of
 Chemistry & Biochemistry, CSUN.

EXTRAMURAL FUNDING

- 2011 National Science Foundation (NSF) - \$240K;
 2007 National Science Foundation (NSF) - \$240K;
 2003 American Chemical Society, Petroleum Research Fund (ACS PRF)
 – \$50K;
 2001 NATO, Physical and Engineering Science and Technology - \$7K;
 1998 Hewlett Packard - \$83K;
 1997 Civilian Research & Development Foundation (CRDF) - \$40K.

MEDIA COVERAGE

- 1994 The Norman Transcript, Norman, OK (article titled “Accelerated
 Course in Organic Chemistry Offered by University of Oklahoma);
 1995-2005 SCOPE, College of Science&Math Newsletter (quarterly; multiple
 publication and presentation reports);
 2003 *Chemical and Engineering News*, Science & Technology
 Concentrate page (Sept 22; p.28) featuring a new reaction
 discovered at CSUN and published in *Organic Letters* 2003, 5,
 3395;
 2004 CSUN Press Release “Cal State Northridge Chemistry Professor on
 a Quest to Defeat Breast Cancer”;
 2004 Northridge Magazine (article titled “Cancer Research and
 Outreach”);
 2005 New Times (Novoye Vremya) newspaper, Yerevan, Armenia; an
 interview on the US and Armenian educational systems and
 reorganization plan of the Armenian National Academy of Sciences;
 2005 Northridge Magazine (article titled “Chemistry Professor on a
 Quest to Defeat Breast Cancer”);
 1998-2008 @CSUN newspaper (multiple presentation and publication
 reports);
 2006-2008 CSUN web banner “Gagik Melikyan is on a mission to find a breast
 cancer cure”;
 2008 The Armenian Reporter, April 2008, No. 58, p.3;
 2009 Asbarez daily newspaper, February 2, 2009; “ARPA Board
 Members Elected as Foreign Members of National Academy of
 Sciences of Armenia”;
 2009 @CSUN newspaper, January 20, 2009; “Chemistry Professor
 Elected to Armenian Science Academy”;
 2009 California Courier, February 5, 2009;
 2009 The Armenian Reporter, February 14, 2009;

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 2011 North Valley Community News, January 2011;
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 2011 In Focus, California Writers Club / West Valley, February, 2011;
 2011 Daily Sundial, CSUN, Northridge, CA; February 2, 2011;
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 2012 *Valley Scribe*, California Writers Club /San Fernando Valley,
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 2012 *Chemical and Engineering News*, June 25, 2012;
 2012 *Speaker Showcase*, Bradley Communications, Broomall, PA;
 2013 *Discussing the Facts vs. Hypes of Antioxidants, Supplements and
 Cosmetics, CSUN Today*, Feb 25, 2013;
 2013 Northridge Magazine, Spring 2013, CSUN, Northridge, CA;
 2013 *Writer's Website of the Month*, The Valley Scribe, California
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 2014 *CSUN SHINE*, Spring 2014, CSUN, Northridge, CA;
 2014 *TheRoundUp*, May 2014, Pierce College, Woodland Hills, CA;
 2015 *CSUN SHINE*, Spring 2015, CSUN, Northridge, CA;
 2015 *The Marquee, News and Views from MTI*, New York, NY;
 2015 *Massis Post*, Thousand Oaks, CA;
 2015 *SCV News*, Santa Clarita, CA;
 2015 *Groong News ANN*, April 6, 2015, Los Angeles, CA;
 2015 *Aravot*, April 2015, Yerevan, Armenia (in Armenian);
 2015 *Asbarez News*, April 13, 2015, CA (in Armenian);
 2015 *USA ARMENIAN LIFE*, April 10, 2015; Glendale, CA;
 2015 *ARPA Institute Newsletter*, April 2015, Tarzana, CA;
 2015 *Novoye Vremya*, May 2015, Yerevan, Armenia (in Russian);
 2015 *Lragyr*, April 2015, Yerevan, Armenia (in Armenian);
 2015 *Tert* media outlet, April 2015, Yerevan, Armenia (in Armenian);
 2015 *Hetq* media outlet, April 2015, Yerevan, Armenia;
 2015 *Armenpress* media outlet, April 2015, Yerevan, Armenia;
 2015 *Armenpress* media outlet, April 2015, Yerevan, Armenia (in
 Russian);
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 2015 *News.am* media outlet, April 2015, Yerevan, Armenia (in
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- 2015 *Digital News World*, April 2015;
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- 2015 *Analitikaua*, May 2015 (in Russian);
- 2015 *Makarats*, May 2015 (in Russian);
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- 2016 <http://www.dormd.net/taking-antioxidant-supplements-may-harm-good/>
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- 2017 http://ru.hayazg.info/Меликян_Гагик_Георгиевич;
- 2017 [http://novostink.ru/diaspora/109043-professor-armyanin-stal-pervym-laureatom-gospremii-uchitel-vdohnoveniya.html;](http://novostink.ru/diaspora/109043-professor-armyanin-stal-pervym-laureatom-gospremii-uchitel-vdohnoveniya.html)
- 2017 *Valley Scribe*, California Writers Club /San Fernando Valley Branch, February 2017.

TV APPEARANCES

- 2009 AMGA channel, Glendale, CA;
- 2011 USArmenia channel, Burbank, CA;
- 2011 CBS KCAL9, Studio City, CA;
- 2012 USArmenia channel, Burbank, CA;
- 2013 The Book Beat, LA TALK LIVE channel, Los Angeles, CA.

RADIO INTERVIEWS

- 2012 DresserAfterDark, BBS Radio;
- 2012 KYNT KSWR radio;
- 2012 KCWR radio;
- 2012 KERN Bakersfield Good Morning News radio;
- 2012 WOCM radio;
- 2012 KCSN-FM radio;
- 2012 KFNX radio;
- 2012 IssuesToday radio;
- 2012 Dr. Joe Radio Show.

PUBLIC APPEARANCES (from a total of 30)

- 2002 Invited speaker, U.S. Civilian Research & Development Foundation (CRDF) and Armenian Diaspora meeting, Glendale, CA;
- 2007 Speaker, Alumni & Friends of Armenian Studies program (AFASP) banquet, CSUN, Northridge, CA;
- 2008 Speaker, Graduation Ceremony, Armenian Studies Program, CSUN, Northridge, CA;
- 2008 Speaker, 25th Anniversary Meeting of the Armenian Studies Program, CSUN, Northridge, CA;

- 2009 Invited speaker, Ferrahian High School, Tarzana, CA;
- 2009 Invited speaker, High School Junior Honor's Day, CSUN, Northridge, CA;
- 2010 Invited speaker, ARPA Institute, book presentation, Thousands Oaks, CA;
- 2011 Invited speaker, Ararat-Eskijian Museum, book presentation, Mission Hills, CA;
- 2011 Invited speaker, Phi Delta Epsilon, book presentation, CSUN, Northridge, CA;
- 2011 Invited speaker, Organization of Istanbul Armenians (OIA), Glendale, CA;
- 2011 Invited speaker, California Writers' Club, San Fernando Valley Chapter, Canoga Park, CA;
- 2011 Invited speaker, Mission Community Hospital, Panorama City, CA;
- 2011 Invited speaker, Provost Colloquium, Jeromy Richfield Award presentation, CSUN, Northridge, CA;
- 2011 Keynote Health Speaker, Filipino American Chamber of Commerce of Orange County (FACCOC), Garden Grove, CA;
- 2011 Keynote Health Speaker, *Staying Healthy and Insights into "Natural" in Health Foods, Remedies, and Cancer Prevention*. Inland Empire Asian Business Association (IEABA), Riverside, CA;
- 2011 Invited speaker, *Health is Wealth*. USANA Inc. Regional Center, Signal Hills, CA;
- 2012 Book Bazaar, California Writers' Club, San Fernando Valley, Woodland Hills, CA;
- 2012 Invited speaker, Armenian Engineers and Scientists of America (AESA), Glendale, CA;
- 2013 Panelist, California Writers' Club, San Fernando Valley, Woodland Hills, CA;
- 2013 Invited speaker, Student Organization for a Holistic Approach to Health and Leadership (SOHHL), Phi Delta Epsilon Fraternity, Chicanos for Community Medicine (CCM) Student Organization, CSUN, Northridge, CA;
- 2013 Guest Speaker, *Women's History Month event*, United States Citizenship and Immigration Services (USCIS) San Fernando Valley Field Office (SFV);
- 2013 Speaker, 30th Anniversary of the Armenian Studies Program, CSUN, Northridge, CA;
- 2013 Guest Speaker, Kiwanis International, Northridge Chapter, Northridge, CA;
- 2014 Invited Speaker, *Toxicity of Heavy Metals and a Long-Term Impact of Irresponsible Mining on Public Health*, CSUN, Northridge, CA;
- 2014 Invited Speaker, *Antioxidants and Natural Supplements: Unraveling the Truth*, Pierce College, Woodland Hills, CA;

- 2014 Invited Speaker, *American Public's Perpetual Struggle Against Harmful Business Practices*, Public Advocacy Group Renaissance Armenia (via satellite), Yerevan;
- 2014 Speaker, *Why "Natural" Is Not Synonymous to "Good" and Harmless*, Vroman's Bookstore, Pasadena, CA;
- 2014 Invited Speaker, *Antioxidants, Supplements, and Cosmetics: Perils of Ignoring Science*, Regional High School Science Teachers' Conference, Ferrahian High School, Encino, CA;
- 2014 Invited Speaker, *Teaching Science in the 21st Century: Challenges and Solutions*, Regional High School Science Teachers' Conference, Ferrahian High School, Encino, CA;
- 2015 Invited Speaker, *The Centennial of Armenian Genocide: Did the World Learn the Lesson, or How to Prevent Genocides in the 21st Century?* CSUN, Northridge, CA.

REVIEWER / EVALUATOR / PANELIST / CONSULTANT / ADVISOR

Reviewer: National Science Foundation (NSF), American Chemical Society, Petroleum Research Fund (ACS PRF), *Organometallics*, *J. Amer. Chem. Soc.*, *Chem. Rev.*, *Org. Lett.*, *Tetrahedron*, *J. Organometal. Chem.*, *J. Cluster Sci.*, *Canadian J. Chem.*; ARPA Institute, Student Innovation Competition; Grant Committee, State Committee on Science and Technology, Armenia; Fellowship Selection Committee – Chemistry, Foundation for Armenian Science and Technology (FAST).

Panelist: National Science Foundation (NSF), Washington, D.C.; California Writers' Club, San Fernando Valley, CA.

Expert/Consultant: Consumer Advocacy Group, Los Angeles, CA; Renaissance Armenia Los Angeles, Los Angeles, CA; Thomson Reuters Expert Witness Services; Round Table Group, Washington, D.C.; National Academy of Sciences (NAS), Armenia; Foundation for Armenian Science and Technology (FAST).

National Registries: *2013-2014 Business Who's Who Registry*; *American Men and Women of Science*.

Scientific Advisory Board: Center for Responsible Mining's Independent Monitoring Technical Advisory Board (IMTAB), American University of Armenia (AUA), Yerevan, Armenia; ARPA Institute, Tarzana, CA.

Thesis committee: Department of Chemistry and Biochemistry, CSUN; Department of Family and Consumer Sciences, CSUN.

Judge: American Association for the Advancement of Science (AAAS) Annual Meeting, Pacific Division, Pomona, CA (2018); Science Olympiad, Armenian

Private/Charter Schools, Los Angeles, CA; CSUN Student Research Symposia, CSUN, Northridge, CA; Sigma Xi Student Research Competition, CSUN, Northridge, CA.

AFFILIATIONS

American Chemical Society; American Chemical Society, Organic Division; American Association for the Advancement of Science (AAAS); ACS Consulting Network; California Faculty Association (CFA); American Association of University Professors (AAUP); California Teachers Association (CTA); National Education Association (NEA); Service Employees International Union (SEIU); California Writers' Club - San Fernando Valley & West Hills Chapters; Independent Writers of Southern California (IWOSC); Institute for Community Health and Wellbeing (CSUN); Book Publicists of Southern California (BPSC); Union of Concerned Scientists (UCS); Public Citizen Foundation; Council on Undergraduate Research (CUR).

EXHIBIT B

Kinetic Analysis of Lead Metabolism in Healthy Humans

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ABSTRACT The steady state kinetics of lead metabolism were studied in five healthy men with stable isotope tracers. Subjects lived in a metabolic unit and ate constant low lead diets. Their intake was supplemented each day with 79–204 μg of enriched lead-204 as nitrate which was ingested with meals for 1–124 days. The concentration and isotopic composition of lead was determined serially in blood, urine, feces, and diet and less commonly in hair, nails, sweat, bone, and alimentary tract secretions by isotopic dilution, mass spectrometric analysis. The data suggest a three-compartmental model for lead metabolism. The first compartment encompasses blood and is 1.5–2.2 times larger than the blood mass. It contains approximately 1.7–2.0 mg of lead and has a mean life of 35 days. This pool is in direct communication with ingested lead, urinary lead, and pools two and three. The second compartment is largely composed of soft tissue, contains about 0.3–0.9 mg of lead, and has a mean life of approximately 40 days. This pool gives rise to lead in hair, nails, sweat, and salivary, gastric, pancreatic, and biliary secretions. Pool three resides primarily in the skeleton, contains the vast quantity of body lead, and has a very slow mean life. Bones appear to differ in their rates of lead turnover. Within the relatively small changes in blood lead observed in the present study, the transfer coefficients between the pools remained constant.

INTRODUCTION

The physiology of lead in humans is currently a subject of considerable interest engendered in part because of the potential toxicity of lead. Despite a number of recent

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studies, many aspects of normal lead metabolism are poorly understood. What is known is largely derived from the study of the time responses of lead levels in body tissues and fluids to changes in lead exposure and uptake. For example, Kehoe (1) and more recently Coulston et al. (2) have conducted a series of long-term studies in which healthy humans were exposed to increased quantities of lead in the diet or atmosphere. Observations in people with increased occupational exposure to lead have also provided data concerning these interrelationships (3). However, there is the possibility that the elevations in lead levels altered the lead physiology in these subjects. Studies involving tracers would enable lead metabolism to be investigated without increasing lead levels.

Hursh et al. have carried out studies with radioactive lead in humans (4, 5). These experiments involved the inhalation, ingestion, and injection of ^{210}Pb which has a half-life of 10 h. Hence, these studies were by necessity of short duration when compared with the characteristic transfer time of lead between major physiological pools.

We report here on the use of stable isotope lead tracers to examine the kinetics of lead metabolism in five healthy adult humans. This method has the advantage of allowing long-term observations without introducing radioactivity or altering lead exposure. A further analytical advantage is that problems from laboratory contamination could be minimized because the isotopic composition of the tracer lead utilized was distinguishable from the common lead in the environment.

METHODS

Five healthy adult male volunteers were maintained in a hospital metabolic unit for periods of 10–210 days. All subjects were apprised in depth of the nature of the experiment and gave informed consent. Subjects were fed diets constant in lead content which were prepared in the metabolic kitchen. In addition, at each meal and at the evening snack, a supplement of an enriched isotope of lead was ingested. The subjects' total daily lead intake was designed to approximate their prestudy levels as estimated from two 5-day fecal collections analyzed before the administration of

TABLE I
Characteristics of the Subjects and Design of the Study

	Subject				
	A.	B.	C.	D.	E.
Age, yr	53	49	27	25	26
Weight, kg	70	89	88	58	84
Average blood lead concentration, $\mu\text{g/g}$	0.25	0.18	0.17	0.20	0.17
Days of study in the metabolic unit*	150	210	10	190	108
Daily intake of tracer, $\mu\text{g/day}$	204	185	68	105	99
Duration of intake of tracer, days	104	124	1	83	10
Usual dietary lead intake, $\mu\text{g/day}$	156	179	142	188	215

* In some subjects collection of specimens was continued after they left the metabolic unit.

the lead supplement. Usually a tracer enriched with ^{204}Pb (89% pure) as nitrate was used (Oak Ridge National Laboratories, Oak Ridge, Tenn.). In three subjects, ^{207}Pb (99.9% pure) as nitrate was used for short periods of time as an additional tracer. After subjects ingested the daily dose of lead tracer, the vial which contained the tracer was rinsed twice with deionized water, and each wash was imbibed by the subject. On several occasions a vial was then rinsed with 6 N HNO_3 , and the lead content of this rinse was measured; less than 0.1 μg of lead was recovered in each washing.

Table I describes characteristics of the subjects, the experimental design, and the quantities of lead ingested. All subjects lived in a room air conditioned without filters to minimize perspiration. Prescribed physical activity was carried out daily. On the first day of the study subjects A. and B. decreased the quantity of cigarettes smoked from about 20 cigarettes to 8 cigarettes/day of a brand which was low in lead content to decrease respiratory intake of lead from cigarette smoke. Subject C. smoked 10 cigarettes/day of a popular brand. Subject D. smoked 20 cigarettes daily of a popular filtered brand for the first 40 days of the study and then stopped completely. Subject E. did not smoke. The lead content of the cigarettes smoked by the subjects before and after the onset of the study, their cigarette ashes, and the unsmoked butts were determined in our laboratory by isotope dilution analysis. On days 109, 75, and 40 of the study, respectively, subjects B., D., and E. entered a room with filtered, low-lead air and lived there for 40, 25, and 50 days, respectively. The changes in smoking habits and airborne lead exposure resulted in alterations in their total blood lead content.

During the study the total content and isotopic composition (IC)¹ of lead were measured in all pooled specimens of urine and feces which were collected continuously, in diets which were prepared in duplicate at weekly intervals, and in whole blood which was collected serially. Feces and urine were each combined into 5–10 day pools. Fecal collections were demarcated with a brilliant blue marker. Blood was collected between 0800 and 0830 from subjects who were fasting since the previous midnight. During the long-term studies, total content and IC of lead were also measured periodically on facial and total body hair (including scalp), nails, induced sweat collected with a plastic body bag, saliva, and gastric, pancreatic, and biliary secre-

¹ Abbreviations used in this paper: EFS, endogenous fecal excretion; IC, isotopic composition.

tions collected by intubation. Pancreatic and biliary secretions were collected after stimulation with secretin and cholecystokinin according to previously described methods (6). In addition, several bone biopsies were obtained from subjects A. and B. from a location 2 cm below either iliac crest. Both cortical tables were removed during biopsy; specimens were immediately washed with saline and acetone, blotted dry, weighed, and then frozen with liquid nitrogen.

Certain specimens were also collected during periods when subjects were not receiving the tracer or were not ingesting a constant diet. Blood and facial hair were not uncommonly collected during such times.

Care was taken to avoid contamination during collection of all specimens. Before aspiration of gastrointestinal secretions, all tubing and flasks were washed with 6 N HCl or 5% HNO_3 (distilled in Teflon) and rinsed with doubly distilled water. Hair samples were rinsed with 2% HNO_3 before spiking. Syringes, needles, and all specimen containers were demonstrated to elute insignificant quantities of lead (less than 0.1 μg).

The concentration and isotopic composition of lead in all specimens were determined by mass spectrometric isotope dilution analysis. Samples were spiked in the laboratory with known quantities of ^{206}Pb before wet ashing with doubly distilled, concentrated HNO_3 (lead content less than 0.7 parts per billion). Lead was extracted with a standard dithizone procedure and added to a silica gel and phosphoric acid mixture. This was loaded on a zone refined and vacuum heated rhenium filament in the thermal emission, solid source, mass spectrometer. Total blanks were typically 0.1 μg of lead. The recovery of lead from spiked samples was determined twice and found to be 92% for blood and 87% for stool. For each analysis a minimum of 10 sets of isotope abundance ratios were collected; the standard deviations of these ratios were usually less than 0.5%.

Certain details of the experimental design and methods of specimen handling in these studies and some aspects of the physiology of lead, such as gastrointestinal absorption, appearance in urine and hair, and compartmentalization within blood have been published previously (7).

Protein, energy, mineral, and vitamin content of the diets were designed to provide at least the minimum daily requirements for these nutrients. During the study, the mean estimated daily energy intake of the subjects was $34 \pm \text{SD } 9$ kcal/kg. The dietary content of certain minerals was analyzed chemically in diets prepared in duplicate at 1–2 wk intervals as previously described (8). Subjects ingested 15 ± 2 g of nitrogen, $3,130 \pm 580$ mg of potassium, $1,240 \pm 50$ mg

of calcium, $1,824 \pm 214$ mg of phosphorus, and 293 ± 24 mg of magnesium. Weight remained stable in all subjects throughout the study. It was concluded that protein and skeletal mass remained approximately constant during the study.

RESULTS

Summary of proposed model. A brief description of the proposed model of lead metabolism is given here to provide a framework for presentation of the results. A more detailed mathematical exposition of the model is given in the discussion. The IC of lead observed in the various tissues and fluids during the study can be understood in terms of a three-compartment model (Fig. 1), although it is likely that there are a multitude of physiological pools of lead.

Compartment one of the three-compartment model can be considered to include primarily blood and other tissues which are in rapid isotopic equilibrium with blood (Fig. 1). Kinetic analysis of the data indicates that this compartment contains about 1.9 mg of lead and receives isotopically labeled lead from the gastrointestinal tract and unlabeled lead from the atmosphere. It exchanges lead with compartments two and three. Lead also moves from compartment one into the urine. Compartment two includes primarily soft tissues and possibly the more actively exchanging parts of the skeleton. It contains approximately 0.6 mg of lead and gives rise to hair, nails, and at least some alimentary tract secretions. Compartment three includes the skeleton and, therefore, most of the lead in the body. The mean life of lead in pool one was 36 ± 5 days. In pool two the mean life varied from 30 to 55 days; in the third pool, it was much greater.

Compartment one. The observed concentrations of

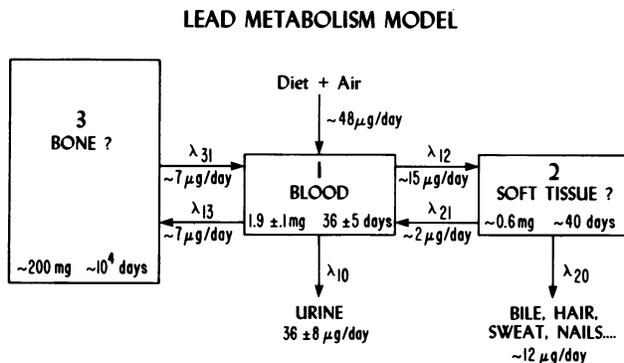


FIGURE 1 A three-compartmental model of human lead metabolism derived from tracer and balance data from five healthy men. The lead content and mean life of each pool and the rates of lead movement between pools (λ) are shown. Numerical values represent the mean values (\pm SD) for all subjects for whom data were available. Loss of lead from the body via pool two (λ_{20}) is from integumentary structures (hair, nails, sweat) and alimentary tract losses, such as salivary, biliary, gastric, and pancreatic secretions.

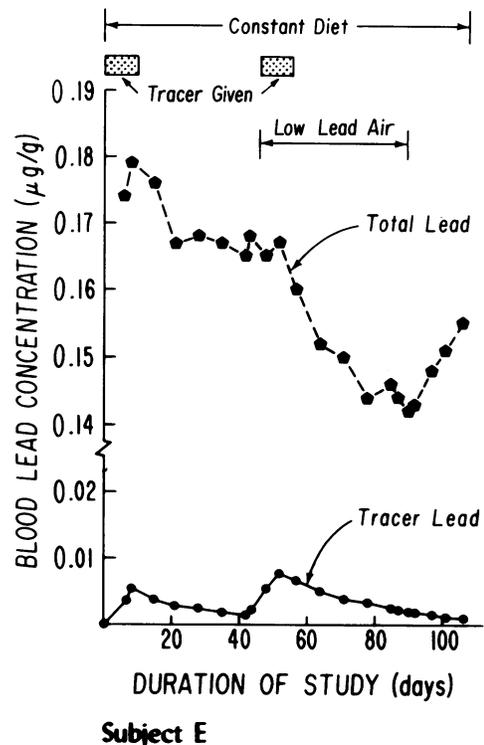
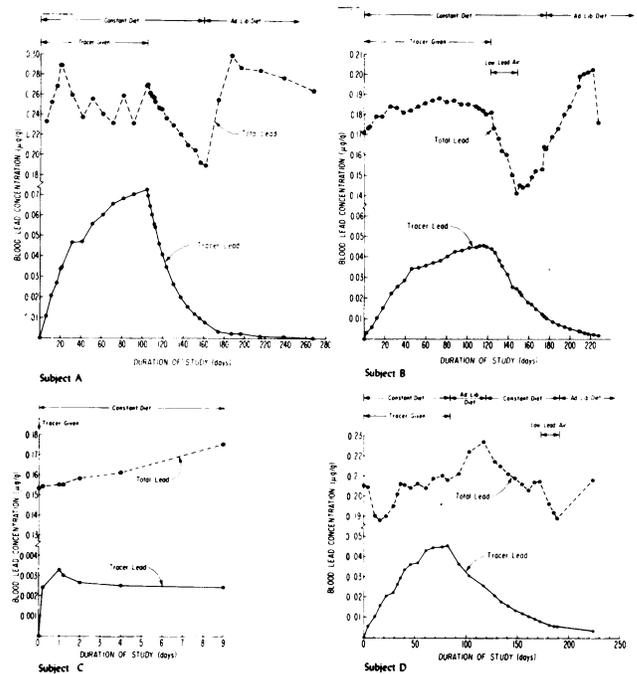


FIGURE 2 Concentrations in whole blood of total lead and tracer lead in five healthy men during ingestion of constant low lead diets supplemented with lead tracer, the same diets without tracer, and ad lib diets. During certain periods of study, some subjects lived in a room with filtered low lead air (subjects B., D., and E.). Attention is called to the break in the vertical scale for each subject and the exaggeration in the magnitude of the vertical or horizontal scales in subjects A. and C.

TABLE II
Size and Exchange Rates of First Pool

	Subject				
	A.	B.	C.	D.	E.
Mass of first compartment, <i>kg</i>	7.4	10	10.1	9.9	11.3
Estimated blood volume, <i>kg</i>	4.9	6.3	6.3	4.6	6.3
Size of first pool, μg	1,860	1,820	1,718	1,993	1,890
Mean life of first pool, <i>days</i>	34	40	37	40	27
Daily input or output from first pool, $\mu\text{g/day}$	54	45	46	50	70
Fraction of output from first pool which goes to urine, %	76	60	78	72	54
Mean urinary output, $\mu\text{g/day}$	41	27	36	36	38

tracer and total lead in pool one are shown in Fig. 2. The administered tracer appears rapidly in blood, and its concentration increases progressively. When the tracer is discontinued, the initial decrease in its abundance was abrupt. In the five subjects it was possible to assess the size and mean life of the pool of lead which was in rapid equilibrium with blood. This was done by fitting the observed changes in tracer lead concentrations in blood with a function containing two exponential terms (equation 8, *vide infra*). The calculated values for the sizes and mean lives of this first pool in the five subjects are shown in Table II.

The mean urinary excretion varied from 27 to 41 $\mu\text{g/day}$. From a comparison of the mean life and size of the first pool and the daily output of lead in urine, it can be calculated that 54–78% of the lead leaving the blood each day passes out of the body in urine (Table II). During the period of study, the IC of urinary lead, measured in urine pools collected for several days, closely resembled the IC of whole blood obtained during that time. Thus, within the time scale of sample collection utilized in the present study, it was not necessary to hypothesize any intermediate pools between blood and urine. Another small and well measured output of lead from the body is the volume of blood sampled periodically during the study. Accurate records of the volume of blood drawn during the course of study indicate that an average of 2.0–2.4 μg of total lead were removed by blood drawing each day. This represents about 4% of the daily output of lead from the first pool.

Compartment two. In contrast to lead lost from the body by urinary excretion and blood sampling, other bodily outputs of lead do not appear to be isotopically equilibrated with whole blood. As shown in Table III, sweat, hair, nails, and digestive secretions become labeled more slowly than blood. Although each substance has a different pattern of tracer uptake, they appear more like each other than like blood. This observation allows the simplifying assumption that for purposes

of kinetic modeling, the origin of these various substances can be assigned to a common physiological pool, distinct from blood. The size and turnover rate of this second pool and its degree of coupling with the blood pool are obtained by fitting the tracer content of blood and the IC of the outputs from the second pool. Table IV shows the parameters of this deeper pool in the three subjects in whom measurements were made. This second pool appears to be smaller and to turn over more slowly than the first pool. Relatively little of the lead in the second pool is returned to blood. About a quarter of the daily amount of lead leaving blood goes to this second pool.

Compartment three. The quantity of lead calculated to reside in these two pools represents a small fraction of the 200 mg of lead which is estimated to reside in the body, primarily in the skeleton (9). Hence a third physiological pool must be construed to exist. Three additional observations from the present study also suggest the existence of a third pool. During both ingestion of the lead tracers and after its discontinuation, the measured biological life of lead in blood is slightly shorter than the urinary and other bodily outputs (i.e., hair, nails, alimentary secretions, sweat) would suggest. This finding suggests the existence of another output of lead from blood. Further evidence for the existence of a third pool is derived from analysis of bone biopsied from the iliac crest (Table V). The tracer was observed in both the dense cortical tables as well as the spongy trabecular bone. It is of interest that the ratio of tracer to total lead was about two or three times greater in the trabeculae than in cortex suggesting a more rapid turnover of lead in trabecular bone. The abundance of tracer in the iliac biopsy was greater than would have been predicted from the estimated movement of tracer into bone and the calculated skeletal mass of the subjects. The rate at which lead moves into the skeleton is taken as the difference between the rate of lead output from pool one and the sum of the lead outputs from

pool one to pool two and to urine (*vide infra*). The estimated movement of total lead from pool one to the skeleton was 9 $\mu\text{g}/\text{day}$ for subject A., 5 $\mu\text{g}/\text{day}$ for subject B., and 4 $\mu\text{g}/\text{day}$ for subject D. A comparison of these calculated rates with the observed concentrations of tracer lead in the iliac biopsies suggests that this portion of the skeleton received lead at approximately three to seven times the average rate of deposition of lead for this deepest body pool (Table V).

The third observation supporting the existence of a third pool is based on evidence indicating that lead moves from the skeleton to blood. After discontinuing

ingestion of the lead tracer, its concentration in the blood does not decrease as rapidly toward zero as would be predicted from a two-pool model. In contrast, the data suggest that there is an internal long-lived source of the tracer. These data were derived from the three subjects who received the tracer for the longest periods of time. The rates of fall of their blood lead tracer after its administration was discontinued as shown in Fig. 3. The evidence for the existence of the input from a third pool is seen most clearly in subject A. His blood tracer concentration had decreased to 0.004 $\mu\text{g}/\text{g}$ 163 days after the dietary tracer was discontinued. This

TABLE III
Lead from Deeper Body Pools

Sample	Subject	Day collected	Measured Pb concentration		Estimated output	
			Tracer	Total	Tracer	Total
			$\mu\text{g}/\text{g}$		$\mu\text{g}/\text{day}$	
Sweat*	A.	134	0.00073	0.005	0.12†	0.8†
	B.	183	0.00037	0.005	0.06†	0.8†
Saliva	A.	50	0.00017	0.0014	0.17†	1.4†
	B.	28	0.00002	0.0010	0.02†	1.0†
		78	0.00017	0.0007	0.17	0.7
		154	0.00010	0.0015	0.10	1.5
Sputum	B.	80	0.00018	0.082	0.01†	4.1†
		125	0.00330	0.012	0.17	0.6
	D.	11-20	0.0012	0.074	0.02§	1.1§
		26-36	0.0015	0.11	0.02	1.4
		46-55	0.0019	0.086	0.01	0.4
Gastric secretion	A.	85	0.0005	0.0025	1.06†	5.3†
		195	0.0002	0.0022	0.43	4.7
	B.	20	0.0008	0.006	1.85†	13.9†
		60	0.0002	0.004	0.45	8.9
		148	0.0006	0.011	1.56	28.5
Bile¶	A.	85	0.0013	0.0063	0.50†	2.4†
		195	0.0003	0.0047	0.12	1.8
	B.	20	0.0009	0.017	0.27†	5.1†
		60	0.0028	0.019	0.86	5.8
		148	0.0044	0.021	1.32	6.3
Pancreatic secretion**	B.	20	0.0001	0.005	0.06†	3.2†
		60	0.0009	0.006	0.57	3.8
		148	0.0006	0.004	0.33	2.2
Total endogenous fecal secretion	A.	130	—	—	1.8	7±2 (SD)
		150	—	—	1.2	7
	B.	130	—	—	2.6	12±3
		140	—	—	1.5	12
		155	—	—	1.2	12
		171	—	—	0.7	12
		227	—	—	0.05	—
	D.	110	—	—	1.7	6±3
		139	—	—	1.0	8

TABLE III—(Continued)

Sample	Subject	Day collected	Measured Pb concentrations		Estimated output	
			Tracer	Total	Tracer	Total
Nails§ (toe and finger)	A.	120	—	8.9	0.0004	0.07
	B.	60	—	22	0.0036	0.7
	E.	20	—	13	—	—
Hair§ (facial)	A.	40	0.05	16.7	0.0036	1.2
		104	0.48	11.8	0.045	1.1
		153	1.00	15.7	0.089	1.4
		181	0.35	16.1	0.03	1.4
	B.	75	0.32	14.5	0.04	1.8
		120	0.55	13.2	0.05	1.2
		220	0.54	11.9	0.05	1.1
	D.	35	0.04	24.7	—	—
		70	0.15	16	—	—
		105	0.34	18.3	—	—
		125	0.6	17.3	—	—
		150	0.36	16.6	—	—
		177	0.24	17.8	—	—
Total body hair§	A.	5–105	—	16.3	—	3.4
	B.	10–179	—	12.2	—	2.7

* Collected during induced profuse sweating.

† Derived from standard estimates of volume produced each day.

§ Daily outputs based on collection of entire specimen.

|| Collected under basal resting conditions.

¶ Collected after administration of cholecystokinin.

** Collected after administration of secretin.

quantity is close to the value of 0.005 $\mu\text{g/g}$ which is predicted from a two-pool model. However, when samplings were continued for a more extended period, the observed values exceeded the concentrations predicted by the two-pool model. After discontinuation of the tracer for 303 days, the blood tracer was 0.002 $\mu\text{g/g}$, while the two-pool model predicted 0.000008 $\mu\text{g/g}$. This additional concentration of tracer can be accounted for by postulating an input of 0.054 $\mu\text{g/day}$ of lead tracer.

Utilizing these inputs of tracer lead to blood, the IC of skeletal lead, as estimated from the calculated loss of tracer from blood to bone (*vide supra*), and the

predicted total lead content of the skeleton, a total of about 6–10 μg of lead can be calculated to move each day from bone to blood. Thus, the changes in concentration of the blood tracer after initiating (*vide supra*) and terminating intake of the tracer indicate that the rate of movement of lead into and out of the skeleton

TABLE V
Lead in Biopsied Iliac Bone and Total Skeleton

	Subject	
	A.	B.
Trabeculae, $\mu\text{g/g}^*$		
Lead tracer	0.075	0.045
Total lead	7.83	4.49
Cortex, $\mu\text{g/g}^*$		
Lead tracer	0.049	0.054
Total lead	14.9	9.10
Estimated tracer lead in total skeleton, μg		
Extrapolation from tracer concentrations in bone biopsies	702	674
Extrapolations from output of tracer from blood	236	103

* Concentrations are expressed on a fresh weight basis.

TABLE IV
Parameters of Second Physiological Pool

	Subject		
	A.	B.	D.
Pool size, μg	260 \pm 100 (SD)	900 \pm 100	550 \pm 100
Mean life, days	30 \pm 4	38 \pm 12	55 \pm 15
Daily input or output, $\mu\text{g/day}$	9 \pm 4	24 \pm 8	10 \pm 3
Fraction of output which goes to first pool, %	28	6	8

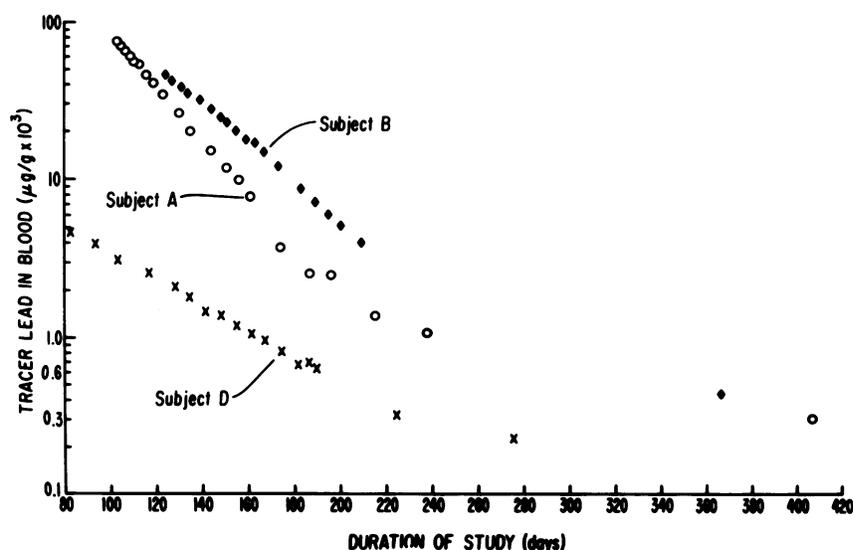


FIGURE 3 The rate of fall of tracer lead in blood after the tracer dosage was discontinued in three subjects undergoing long term studies. The first blood level depicted for each subject indicates the beginning of the first day without tracer. The data are presented logarithmically, and the changes in the slopes provide evidence that tracer lead is entering blood from deeper body pools.

was approximately the same. These estimations of lead movements, which were made by two sets of relatively independent observations, suggest that lead balance for the skeleton was within about 4 µg/day of equilibrium.

Intestinal absorption and excretion of lead. The rates of absorption of lead tracer from the gastrointestinal tract were determined by measuring the difference between intake and fecal output of tracer lead after correcting the output for endogenous fecal excretion (EFS) (Table VI). Knowledge of real absorption (input plus EFS minus output) is necessary to assess the magnitude of body lead pools and rate constants. Initially, no tracer lead is excreted by the body into the feces because the source of these secretions has not yet become labeled. Hence, only unlabeled lead is secreted. Thus adjustment of calculated absorption of tracer lead for EFS is initially nil. However, after a

few months of continuous tracer intake, bile and gastrointestinal secretions were found to contain appreciable amounts of tracer lead (*vide supra*), and EFS of tracer lead at this point may have contributed up to a few micrograms per day to total fecal output of tracer.

The calculated amount of tracer lead in feces which is derived from unreabsorbed lead in bile and other bodily sources rather than from unabsorbed tracer lead is based on a model-dependent extrapolation of two observed quantities: (1) the tracer lead content of specific gastrointestinal secretions measured on a few occasions and (2) the delayed disappearance of the tracer from feces after its discontinuation from the diet. The former set of measurements indicates how the relative amounts of tracer and total lead in the secretions change with time. Moreover, these measurements can be used to estimate the total daily lead output. However, these mea-

TABLE VI
Intestinal Absorption and Excretion of Lead Tracer

	Subject				
	A.	B.	C.	D.	E.
²⁰⁴ Pb Tracer intake, µg/day of lead tracer	204.4±0.2(SD)	185±0.03	67.8±0.03	104.8±0.03	99.1±0.03
Fecal output, µg/day of lead tracer	183.3±1.3	174±0.8	58.5±1.2	94±1.4	90.1±1.1
Endogenous excretion, µg/day of lead tracer	1±0.3	1±0.2	0	0.6±0.3	0
Quantity of tracer absorbed,* µg/day of lead tracer	17.5±1.5	12±1	9.3	11.4±1.4	9.0±1.1
Percent of tracer absorbed*	8.5±0.7	6.5±0.5	13.7	10.9±1.3	9.1±1.1

* Corrected for the endogenous excretion of tracer (see text).

surements represent only a few accessible sources of EFS (salivary, gastric, biliary, and pancreatic) collected under conditions of stimulated secretion (Table III). In contrast, the delayed disappearance of tracer from feces can be used to calculate the amount of tracer lead which is excreted from all internal sources of fecal lead.

In two subjects (A. and B.), a second isotope tracer, ^{207}Pb as the nitrate, was administered for 10 days each to differentiate between endogenous excretion of lead tracer and delayed passage of unabsorbed tracer. Ingestion of ^{207}Pb and the first tracer, enriched in ^{204}Pb , were discontinued concurrently. Fecal excretion of the second tracer was not detectable 20 days after it was discontinued. Hence, excretion of the first tracer more than 20 days after ingestion was terminated was considered to represent endogenously excreted lead. In the three subjects for whom EFS was reported (Tables III and VI), EFS of tracer lead was determined in specimens collected more than 20 days after stopping the tracer. In these calculations, the assumption is made that the rate of reabsorption of endogenously excreted lead is similar to that of ingested lead nitrate tracer.

DISCUSSION

The formula which was used to describe this model was based upon the following considerations: the rates of change of the concentrations of a set of isotopically identifiable species of lead in each of a group of interconnected compartments can be expressed in terms of a set of coupled first order differential equations. One such equation is as follows:

$$\frac{dX_i}{dt} = \frac{A_i}{M_i} - \lambda_i X_i + \sum_j \lambda_{ji} X_j \frac{M_j}{M_i} \quad (1)$$

Where X_i is the concentration of a species in compartment i ($\mu\text{g/g}$)

M_i is the mass of compartment i (g)

A_i is the rate at which species X enters compartment i directly from outside the body ($\mu\text{g/day}$)

λ_i is the rate constant for the movement of lead either into or out of compartment i (day^{-1}). It is the reciprocal of the mean residence time for lead in the compartment.

j refers to each pool other than i

$$M_j \sum_i X_i$$

is the quantity of lead in pool j (i.e., its size) λ_{ji} is the rate constant for movement from compartment j to i (day^{-1}) with the notation that

$$\lambda_i = \sum_{j=0} \lambda_{ij} \quad (2)$$

This set of expressions has the form of linear equations.

However, insofar as the total lead content is maintained constant, the application of equation (1) to the modeling of lead metabolism is not based upon the assumption that the flow of lead into or out of a compartment varies linearly with the lead level. Rather it is only assumed that the relative amounts of the various isotopes of lead leaving a compartment are proportional to their relative abundances inside the compartment. In other words, a biological compartment or system would not be able to distinguish one isotopic species from another or handle them differently. Development of this model is also based on the assumption that the sizes of the pools are constant during the period of study, i.e., there is mass equilibrium. As discussed in Methods, clinical evaluation and dietary intake of the subjects suggested that the protoplasmic and skeletal mass of the subjects were in neutral balance. The λ 's are considered to be independent of time. In addition, the model appears to fit the experimental data equally well over the range of concentrations of lead found in the present study (*vide infra*). Hence for this study the λ 's are also considered to be independent of the total lead content in a compartment. However, it is possible that with a wider range of lead concentrations the λ 's may vary. As is usual with compartmental analysis, a compartment or pool is considered to be isotopically well mixed.

Because of the slow turnover of compartment three, only a negligible quantity of tracer lead from this pool moves back into blood during the course of the experiment. For the first 100–200 days of each experiment, compartment three can therefore be considered as a time-independent source of normal lead and as a sink for labeled lead. According to the design of this study, only compartment one receives the lead tracer directly from outside the body. These findings allow equation (1) to be simplified. Thus, the differential equations for the change in the concentrations of tracer lead in two time-dependent compartments (one and two) would become

$$\frac{dX_1}{dt} = \frac{A}{M_1} - \lambda_1 X_1 + \lambda_{21} \frac{M_2}{M_1} X_2 \quad (3)$$

$$\frac{dX_2}{dt} = \frac{M_1}{M_2} X_1 \lambda_{12} - \lambda_2 X_2 \quad (4)$$

Equations (3) and (4) can be more conveniently expressed in terms of the measurable blood lead concen-

tration X_b by substituting $X_b = \frac{X_1}{K}$ where the scale

factor K is the ratio of the mean concentration of lead in compartment one to that in blood.

General solutions to equations (3) and (4) have been derived giving X 's as a function of time in terms of λ 's,

M 's, and A ; they are of the form

$$X_b = C_{11}e^{-r_1t} + C_{12}e^{-r_2t} + C_{13} \quad (5)$$

$$X_2 = C_{21}e^{-r_1t} + C_{22}e^{-r_2t} + C_{23} \quad (6)$$

The coefficients C are known functions of the parameters, λ 's, M 's and A , and the initial conditions, and r_1 and r_2 are the roots of the quadratic

$$(r - \lambda_1)(r - \lambda_2) - \lambda_{12}\lambda_{21} = 0 \quad (7)$$

In general when $t = 0$, $X_b = X_0$, and $X_2 = Y_0$, equation (5) would become

$$X_b = \frac{1}{(r_1 - r_2)} \left\{ \left[(r_1 - \lambda_2) \left(X_0 - \frac{A}{M_1 K r_1} \right) - \frac{M_2}{M_1 K} \lambda_{21} Y_0 \right] e^{-r_1 t} + \left[(\lambda_2 - r_2) \times \left(X_0 - \frac{A}{M_1 K r_2} \right) + \frac{M_2}{M_1 K} \lambda_{21} Y_0 \right] e^{-r_2 t} \right\} + \frac{A}{M_1 K} \frac{\lambda_2}{r_1 r_2} \quad (8)$$

The observed concentrations of the tracer lead in blood and other tissues and fluids enable one to apply equation (8) and an analogous equation for compartment two to calculate the pool sizes, mean lives, and exchange constants as described in the results. Table VII indicates the measured concentrations of tracer lead in blood of the five subjects and the predicted values for each specimen calculated from the compartmental model described in equation (8).

It should be emphasized that during ingestion of the lead tracer, the changing concentrations of tracer in blood could be adequately described by a two pool model. In this simplified model, the second and third pools would be combined. In the present study, the data which distinguished the second from the third pools were (1) the changing rates of disappearance of the tracer lead from blood after discontinuing the tracer and, more importantly, (2) the observation that the IC of lead in hair, nails, and alimentary tract secretions did not resemble that in either blood or bone. Indeed, it was not possible to distinguish three distinct pools in the two subjects who were studied less extensively.

As previously mentioned the calculated combined amount of total lead in pools one and two is approximately 3 mg. This is markedly less than the 10–30 mg of lead found in soft tissues at autopsy (9). This finding indicates that most of the lead in soft tissues does not exchange with blood during the several-hundred-day period of study. Hence, according to the three pool model, this nonexchangeable soft tissue lead would be consigned to the third pool. In the present study, there

was no relation between the quantity of lead in pools one and two and the age of the subjects. These findings are consistent with those of Schroeder and Tipton that soft tissue lead content does not vary closely with age (9).

The size of the first, most labile, compartment is 1.5–2.2 times the estimated blood mass, and accounts for 11–17% of the body mass of the subjects. The mean life of pool two is appreciably shorter than the mean life of the red cell, about 120 days (10). Since approximately 90% of the lead in blood resides in red cells (11), it may be inferred that lead enters and leaves red cells several times during their lives. The results from the present study and other data concerning tracer lead in blood and urine (11) support this concept. Urine and blood lead are essentially in isotopic equilibrium (12), and since most of the lead in urine is probably filtered (13), it seems evident that lead may readily enter and leave the red cell. In vitro studies have also shown a rapid uptake of tracer lead by erythrocytes (14).

There is an important question concerning the extent to which values for the rate constants (λ 's) for lead transfer are dependent on blood levels, degree of exposure, or body burden of lead. Although the present study was designed so that blood lead levels would not vary greatly, the data provide some evidence that these rate constants are independent of changes in blood lead levels over at least a small range of values.

In subject B., the blood lead decreased to 0.15 and then increased to 0.18 $\mu\text{g/g}$ between days 130 and 180 (Fig. 2). During this time, the biological decay rate for the tracer in blood remained fairly constant as seen by the slope in Fig. 2. Similarly for subject D., the blood lead fell to 0.205 and rose to 0.225 $\mu\text{g/g}$ between days 90 and 180 while the tracer disappeared at a constant rate. In no subject did the transfer coefficients appear to vary during alterations in blood lead concentrations. Hence, it may be inferred from these observations that within the range of commonly found blood lead concentrations, changes of 10–20% do not observably alter the rate constants. These findings as well as previously reported data (11) indicate that the blood lead and the quantities of lead absorbed from the gastrointestinal tract, excreted in urine, and transferred to deeper body pools vary linearly with dietary lead exposure.

Tola et al. have described the response of blood lead to excessive occupational lead exposure (3). It is of interest that they found the characteristic time for the elevation of blood lead levels to be approximately 1 mo. This corresponds closely to the mean life of the first pool observed in the present study, about 35 days. Thus, the transfer coefficients for lead observed in this study may remain constant over a much wider range of blood lead levels.

It is of interest that in the present study the lead con-

TABLE VII
Observed and Predicted* Concentrations of Tracer Lead in Blood

Subject A.			Subject B.			Subject C.			Subject D.			Subject E.		
Day‡	Observed§	Predicted	Day‡	Observed§	Predicted	Day‡	Observed§	Predicted	Day‡	Observed§	Predicted	Day‡	Observed§	Predicted
<i>µg tracer lead / g whole blood</i>														
6	0.0108	0.0130	4	0.0033	0.0044	1	0.0033	0.0033	4	0.0060	0.0044	7	0.0036	0.0049
11	0.0207	0.0219	7	0.0055	0.0074	2	0.0027	0.0032	11	0.0109	0.0111	8	0.0054	0.0055
16	0.0269	0.0294	12	0.0103	0.0119	4	0.0025	0.0029	16	0.0157	0.0152	15	0.0039	0.0041
20	0.0338	0.0346	18	0.0152	0.0167	9	0.0025	0.0026	22	0.0207	0.0195	21	0.0029	0.0033
21	0.0345	0.0357	26	0.0223	0.0220				29	0.0223	0.0238	28	0.0025	0.0025
31	0.0466	0.0457	32	0.0257	0.0253				33	0.0263	0.0259	35	0.0019	0.0020
41	0.0470	0.0529	39	0.0285	0.0287				36	0.0295	0.0274	42	0.0015	0.0015
51	0.0559	0.0581	46	0.0344	0.0315				40	0.0337	0.0292	43	0.0022	0.0015
61	0.0603	0.0619	53	0.0349	0.0338				46	0.0362	0.0316	48	0.0055	0.0046
71	0.0656	0.0647	60	0.0359	0.0358				53	0.0370	0.0339	52	0.0076	0.0076
81	0.0684	0.0668	67	0.0373	0.0374				61	0.0433	0.0362	57	0.0063	0.0063
91	0.0703	0.0683	74	0.0382	0.0388				68	0.0445	0.0378	64	0.0050	0.0049
104	0.0724	0.0697	81	0.0403	0.0400				77	0.0448	0.0396	71	0.0038	0.0038
105	0.0698	0.0674	88	0.0406	0.0409				82	0.0452	0.0404	78	0.0029	0.0030
107	0.0646	0.0632	95	0.0433	0.0418				93	0.0373	0.0314	85	0.0025	0.0023
109	0.0601	0.0592	102	0.0442	0.0425				103	0.0307	0.0250	87	0.0022	0.0021
111	0.0556	0.0555	109	0.0448	0.0430				117	0.0262	0.0183	90	0.0020	0.0019
112	0.0540	0.0537	112	0.0453	0.0433				128	0.0209	0.0143	92	0.0019	0.0017
116	0.0460	0.0473	116	0.0456	0.0435				134	0.0170	0.0125	97	0.0016	0.0014
119	0.0410	0.0430	119	0.0450	0.0437				141	0.0156	0.0108	101	0.0012	0.0013
123	0.0349	0.0378	124	0.0459	0.0440				148	0.0132	0.0092	106	0.0010	0.0010
130	0.0265	0.0303	127	0.0421	0.0409				155	0.0113	0.0079			
137	0.0202	0.0243	131	0.0385	0.0372				161	0.0105	0.0070			
144	0.0155	0.0196	134	0.0357	0.0346				167	0.0090	0.0061			
151	0.0120	0.0157	139	0.0317	0.0306				172	0.0080	0.0055			
156	0.0100	0.0135	144	0.0279	0.0271				182	0.0064	0.0045			
161	0.0080	0.0115	148	0.0248	0.0246				186	0.0048	0.0041			
174	0.0033	0.0077	151	0.0230	0.0229				188	0.0046	0.0039			
187	0.0026	0.0052	155	0.0205	0.0208				224	0.0036	0.0019			
196	0.0025	0.0039	159	0.0180	0.0189									
215	0.0012	0.0022	163	0.0170	0.0171									
238	0.0010	0.0011	167	0.0149	0.0156									
267	0.0004	0.0005	173	0.0123	0.0134									
407	0.0002	0.000008	175	0.0114	0.0128									
			177	0.0104	0.0122									
			183	0.0087	0.0106									
			189	0.0071	0.0091									
			195	0.0060	0.0079									
			200	0.0051	0.0070									
			209	0.0040	0.0056									

* Predicted from the mathematical model of lead metabolism (see text).

‡ Ingestion of lead tracer began on day zero. In addition, in subject E. lead tracer was discontinued on day eight and administered again from days 42 through 51

§ Each observed value was analyzed in blood which was drawn in fasting subjects between 0800 and 0830 on the indicated day.

|| Tracer discontinued after blood was drawn on this day.

centrations in sweat were determined to be about 7 µg/l which is about 20% of the concentration in urine. This finding is in contrast with previous reports that the lead levels in sweat and urine are equal (15). The present data also indicate that in contrast to previous comments (15) salivary, gastric, pancreatic, and biliary secretions all contribute to the excretion of lead in the alimentary tract. The product of the respective lead concentrations and the predicted daily volume of each of these secretions (16) indicates that the gastric juice may be a major source of endogenous fecal excretion (Table III). It is possible that these results may not completely reflect the normal state as secretin and cholecystokinin were used to stimulate secretions. More-

over despite careful collection techniques, saliva is particularly subject to contamination from the urban atmosphere.

The results of this study differ markedly from the pattern of lead handling reported in rodents. Rats were studied after a single intravenous injection of ²¹⁰Pb (17, 18). After injection, there was a more rapid clearance of lead from blood, with an excretion coefficient of 0.2/h. In contrast to adult humans, more lead was excreted in feces and transferred into the skeleton. These differences may be a result of the design of the experiment; the rats received 25–250 µg of lead carrier, which may have greatly altered the normal physiological handling of lead and affected red cell survival. In other

experiments where rats and hamsters inhaled radioactive lead (19), the bodily distribution of tracer lead was found to differ from humans. The animals had a higher percentage of the administered tracer in the kidneys and only half as much in erythrocytes as compared to humans. Their clearance of lead from blood was also more rapid.

In these latter studies the total lead intake was not substantially increased, and therefore their lead metabolism was probably not perturbed. Hence, these observations may indicate a difference between rodents and humans in the physiological handling of lead.

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