Biomarkers and Risk Assessment for Chromium(VI)

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Background

- Toxicity of oxidation states of Chromium (Cr)
  - Cr(III) is relatively nontoxic, poorly absorbed, little crosses cell membranes, & may be an essential element
  - Cr(VI) is strong oxidizing agent: toxic and carcinogenic; crosses cell membranes

Public Health Risks

- Cr(VI) is public health concern: Superfund site contaminant
- Current Risk Assessments based on extrapolations: high-to-low concentrations and/or animal-to-human

Study Approach

- Measure exposure levels, internal dose, markers for biologically effective dose & genotoxicity.
- Ultimate goal: determine which biomarkers are useful quantitative indicators of Cr(VI) exposure at low levels for future epidemiology or surveillance

Intermediate Objectives for Biomarker Validation & Utility

- Examine the reproducibility of each biomarker (intraindividual vs. interindividual variability)
- Measure sensitivity of biomarker at progressively lower levels
- Examine the specificity of the biomarker (? affected by smoking, diet, age, other metal exposures?)

Exposure Biomarkers

- Plasma Cr – Cr(III), some Cr(VI)
- Erythrocyte or Lymphocyte Cr – source mainly Cr(VI) [but is reduced to Cr(III) within the cell]
- Dose-response may be affected by plasma reduction capacity

Markers of Biological Effects or Susceptibility

- DNA-protein cross-links (DPC) in leukocytes (assess biologically effective dose?)
- Comet assay – detects DNA single-strand breaks or incomplete repair, alkali-labile sites, DNA-DNA or DNA-protein cross-linking
- Susceptibility markers of extracellular reduction capacity
  - Ratio of Cr in erythrocytes to that in plasma
  - Plasma ascorbate levels
  - Plasma oxidative status

Methods & Procedures – I.

- Identified factories with Cr exposure
- Conducted walk-throughs to select factories
- Talked with management & then employees about the study
- Administered questionnaire re: smoking, health status, etc. so as to select subjects

Methods & Procedures – II.

- Physical exam
- Personal exposure monitoring – one 8 hr shift
  - Used personal monitor with pump
- Urine sample at end of workday – for cotinine & creatinine
- 10 ml blood sample – separated into plasma, lymphocytes & erythrocytes
- For 8 subjects monitored & blood on 3 successive Mondays

Methods & Procedures – III.

- In year 1, obtained 25 exposed & 25 unexposed (farmers >50 miles away)
- In year 2, just completed obtaining exposure & bloods on another 125 exposed & 30 unexposed
- Subjects in year 1 were mostly highly exposed, those in year 2 have a broad range of lower exposures
- Each year spent >1 mo. in China collecting data

Principal Statistical Analyses

- Examine reproducibility of biomarker
- Determine initial sensitivity of biomarker assay to detect high-exposure effects
- Examine slope & shape of exposure-response curve
- Evaluate sensitivity of biomarker at lower exposure levels

Statistical Analyses – Other Considerations

- Control for possible confounding variables: age, sex, smoking
- For Cr(VI), evaluate & adjust for exposures to Cr(III) & to nickel
- Is Cr(VI) exposure-response relation modified by plasma reduction capacity, serum vitamin C or oxidative status?

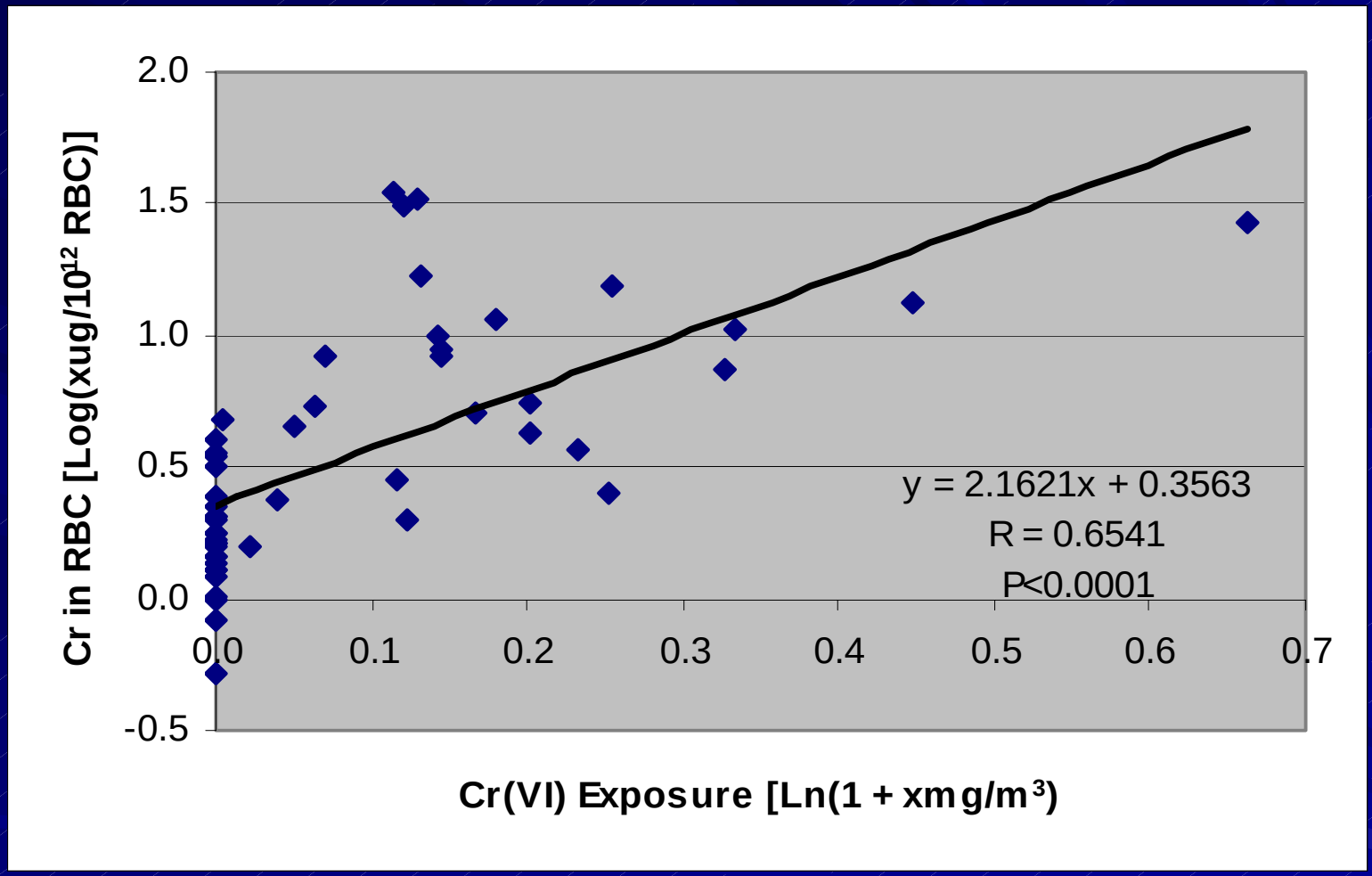

Fig. 1 Correlation between personal exposure and Cr levels in RBC

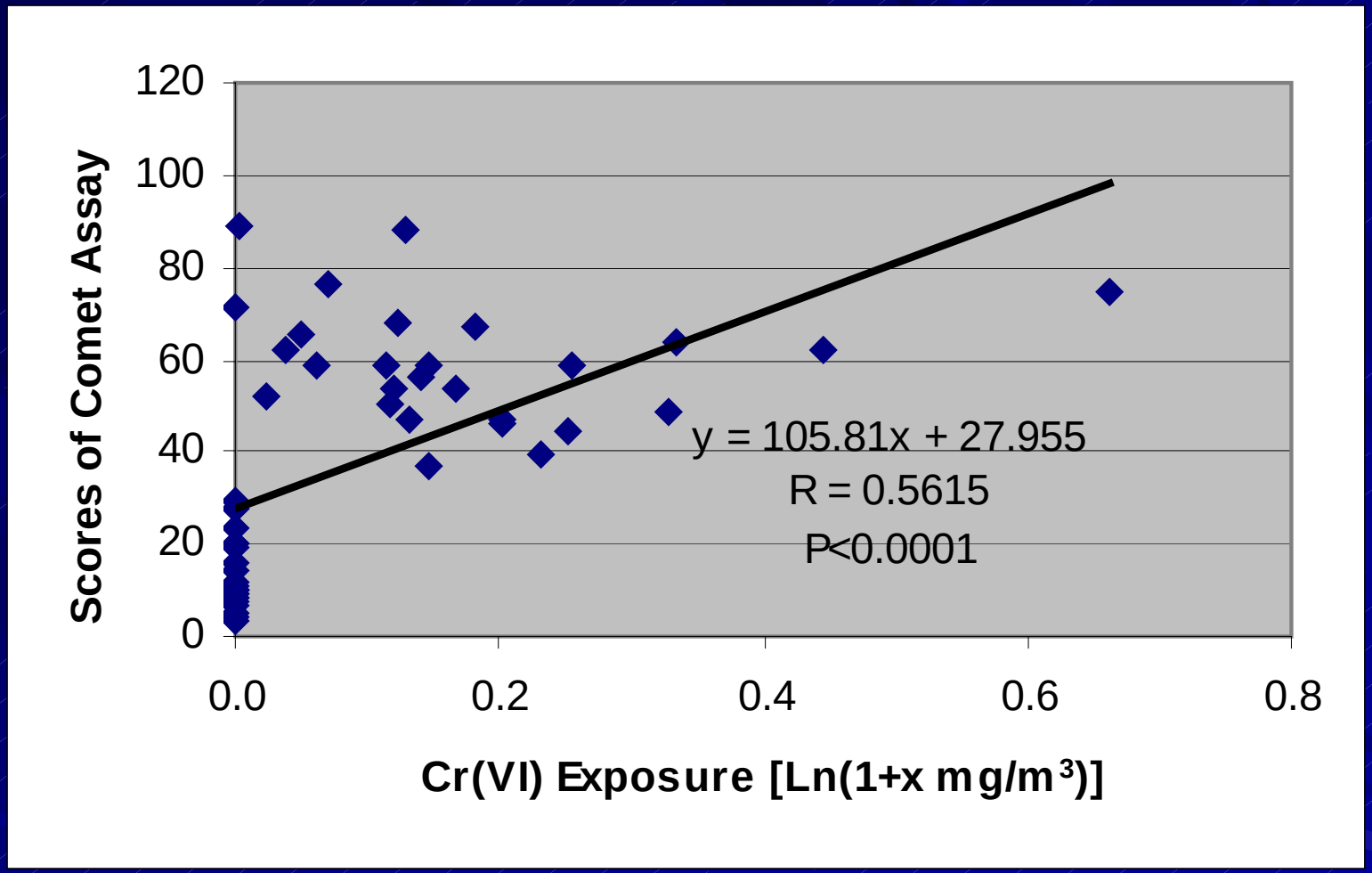

Fig. 3 Correlation between comet scores and personal exposure to Cr(VI)

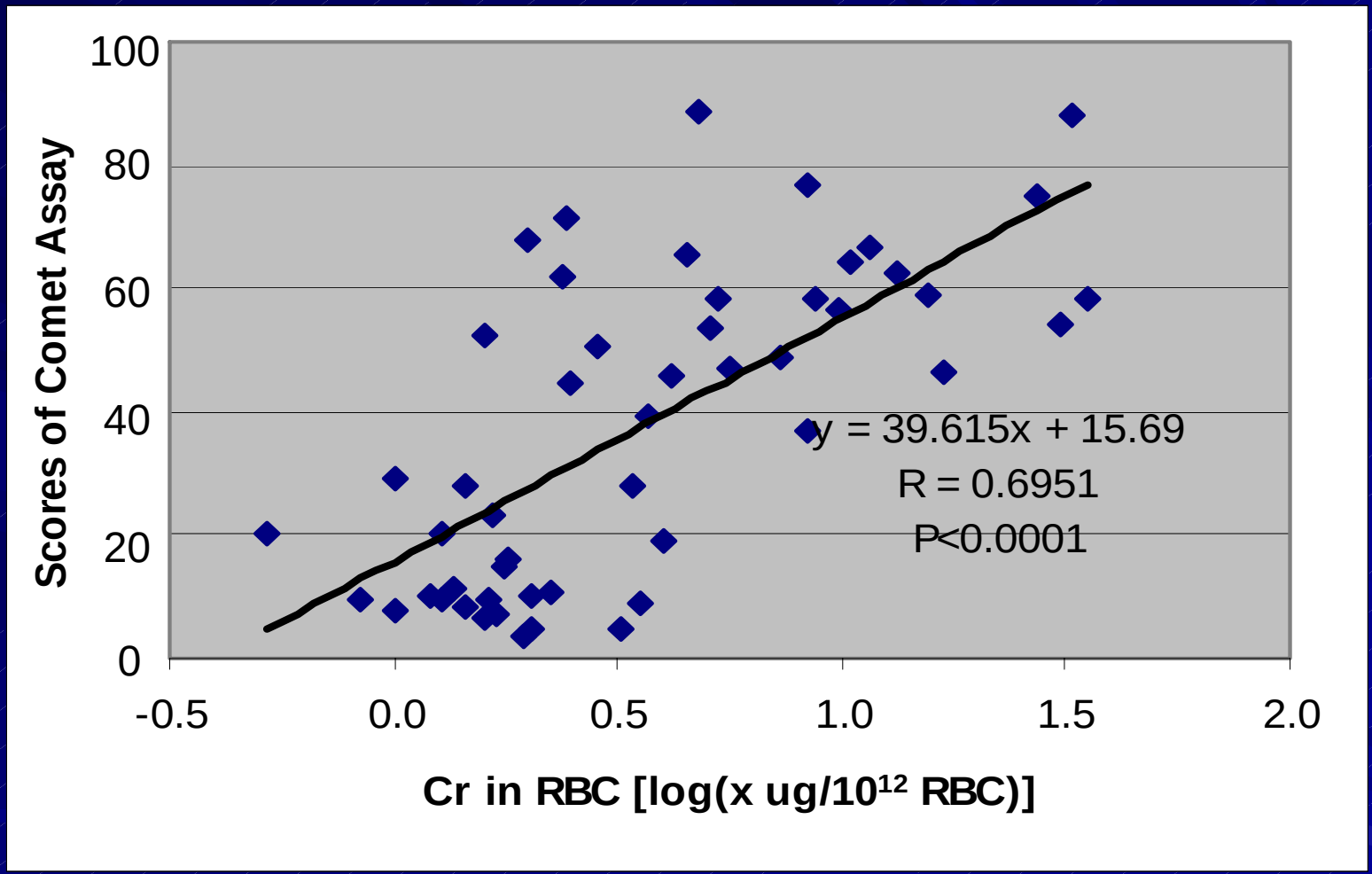

Fig. 4 Correlation between comet scores and Cr levels in RBC

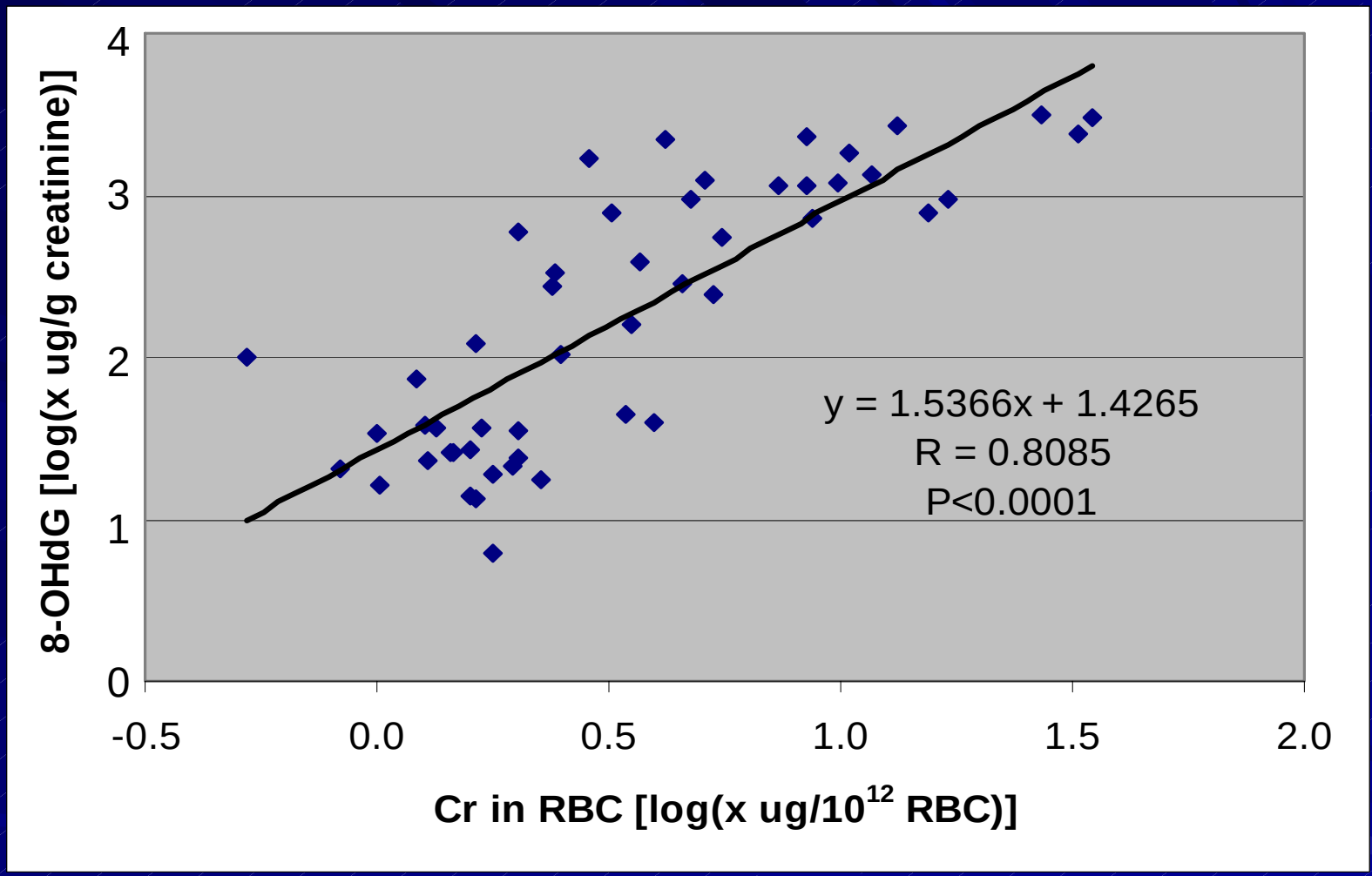

Fig. 6 Correlation between urinary 8-OHdG and Cr levels in RBC

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