How is ORD Leading the Effort to Improve Our Understanding of the Aging Population's Susceptibility to Environmental Stressors?

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Contributing Organizations: NHEERL, NERL, NCEA Office of Pesticide Programs

B·O·S·C HUMAN HEALTH PROGRAM REVIEW

RESEARCH TRIANGLE PARK, NORTH CAROLINA JANUARY 13-15 2009

RESEARCH & DEVELOPMENT

LTG 3 Poster 10

Science Questions

What is ORD doing to improve our knowledge base about susceptibility and vulnerability in the aging population? ORD's exposure-dose-response approach summarizes existing information and generates new data on toxicants that older adults may be exposed to, the activities that bring them into contact with the toxicants, the internal toxicant distribution and transformation, and the health effects resulting from exposure.

How do we measure susceptibility and vulnerability?

•Increased environmental contact
•Increased internal dose
•Shift in the dose-response
•Increased duration of effect
•Increased time to recover
•All of the above

What should we do about variability? Variability is often considered a hallmark of aging, and could mask toxicant effects when large interindividual differences in sensitivity exist. For the aging population, accurate estimates of variability may be especially important in estimating risk.

How could the Agency use these data? The Agency needs to know whether current standards protect the aging population, or whether additional measures must be taken.

Research Goals

•Implement a research program that addresses needs identified in EPA's Aging Initiative regarding the environmental threats to older adults.

•Integrate information on exposures, activity patterns, toxicant kinetics and health outcomes in older adults through literature searches and laboratory research.
•Develop models that incorporate variability in order to estimate adverse effects in the diverse population of aging adults.
•Determine whether classification of the aging population, based on exposures and/or health conditions, can be used to replace chronological age for identifying specific at-risk groups.

www.epa.gov/aging

Findings and Conclusions

❖**Significant differences in exposures and activity patterns may increase susceptibility in the aging population.**

❖ **Changes in physiological parameters, including metabolic activity, are much greater early in development than in later life, but can nonetheless influence tissue dosimetry and residence time.**

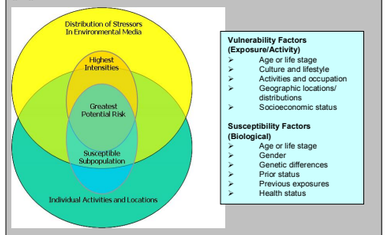
❖**Aging-related toxicant effects are endpoint-specific: Effects are either greater than or equal to those in younger adults, but not less.**

❖**Modeling aging-related toxicant effects underscores the importance of incorporating variability for accurate estimates of risk.**

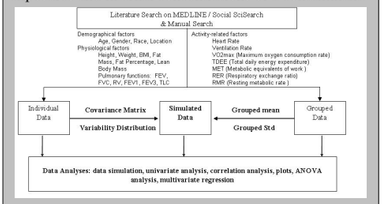
Methods/Approach

What is ORD doing to improve our knowledge base on susceptibility and vulnerability in the aging population?

The Consolidated Human Activity Database (CHAD;www.epa.gov/chadnet1) is drawn from representative samples of the population to characterize the environments and activities where people live and work. CHAD has over 35,000 person-days of data, including 6000 person-days compiled recently for older adults (up to age 90).
CHAD, coupled with information on exposure and physiological factors, can help pinpoint susceptible populations.



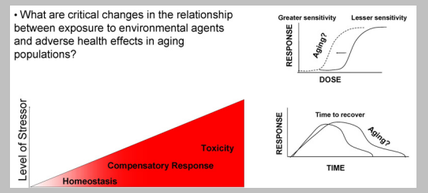
Summarizing physiological data for aging adults provides a critical link between environmental exposures and internal concentrations of a contaminant.



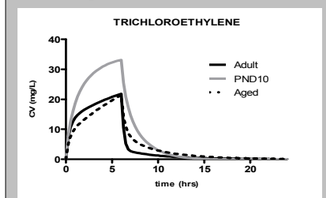
Physiological variables differ between aging individuals even when chronological ages are similar.

Variable/ Health Condition	All (n=567)	Healthy (n=454)	Heart (n=20)	Comorbid (n=57)	Lung (n=9)	Hormone (n=7)	Athlete (n=20)
VO2 peak/kg (ml/min/kg)	28.2	27.9	15.5	21.2	14.2	28.3	48.5
HR peak (beat/min)	152	151	132	149	132		170
HR rest (beat/min)	65.3	67.9	74	67.7	68	58	49.4
VE max (l/min)	69.4	59.7		57.7	91		129.2
Age	67.9	68.2	67	70.2	63.6	62.4	59.5
BMI (kg/m2)	26.7	26.7	26.9	26.9	26.4	25.5	23.1

How do we measure susceptibility?

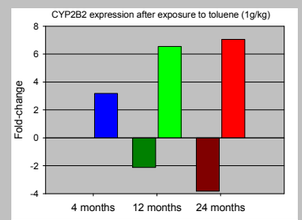


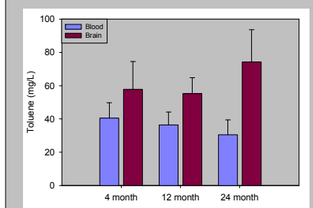
Changes in metabolism are greater during early development than in later life.



The higher concentration in neonates is likely due to a higher ventilation rate and lower metabolic capacity.

Decreases in baseline metabolic activity (negative-fold changes) in later life are still sensitive to toxicants

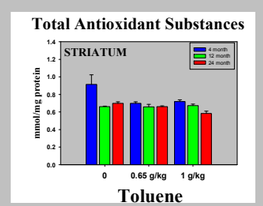


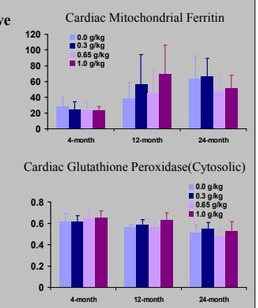


Decreased clearance in old age could prolong residence time of toxicants in target organs.

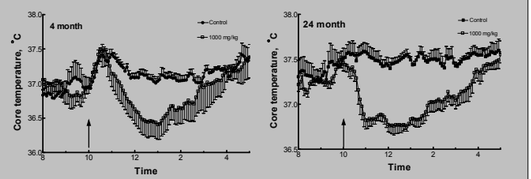
Studies compared toluene effects on CNS, cardiovascular and autonomic function across several ages in Brown Norway rats.

Aging heart and brain show oxidative stress. Toluene had small effects on many biochemical measures.

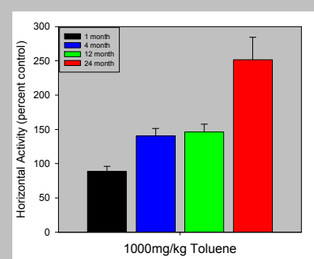




Toluene produced larger and more long-lasting decreases in core body temperature in senescent than in young adult rats.



The prolonged hypothermia in old rats may be related to the increase in brain toluene concentration.

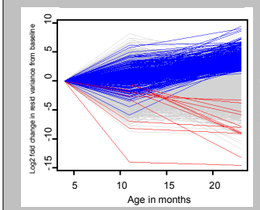


Aging increased sensitivity to toluene-induced hyperactivity. Variability also increased in old age.

What should we do about variability?

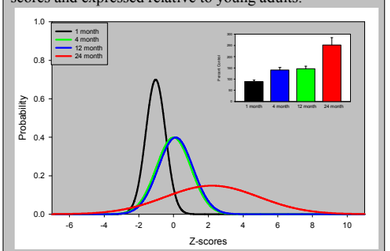
Current risk assessments do not directly incorporate interindividual variability. Increased variability in either baseline function or toxicant response would likely confound any evidence of increased risk in the aging population. For example, day-to-day correlations in CHAD are low, with considerably more variability in older adults.

Laboratory studies can provide valuable information on individual differences.



Variance in gene expression predominantly increased with age in rat retinae.

Aging rats were more variable in their response to toluene. Data for individual rats were transformed to z-scores and expressed relative to young adults.



Increased variability in a susceptible population can mean more individuals are at risk than estimated by current methods.

Toluene z-scores

Age	Mean	Standard Deviation
Adolescents	-1.03	0.6
Young adults (reference group)	0.00	1.0
Middle-age	0.12	1.0
Senescent	2.22	2.7

For z=1.65 (P=0.05), increase in risk:
•Adolescents = 0%
•Young adults = 0%
•Middle-age = 22%
•Senescent = 1330%

Impact and Outcomes

How could the Agency use these data?

•CHAD has been used in several NAAQS reviews and risk assessments for hazardous air pollutants. Expansion of the database to include older adults will reduce current uncertainties and insure consideration of this population in decision making.
•ORD research highlights the importance of including the aging population in studies on toxic substances, and the need to incorporate analyses that can quantify variability in sensitivity.
•Creation of publicly accessible databases and other tools for modeling the potential risks of exposure in older adults complements OCHPEE's activities in making educational materials publicly available that cover risk awareness and reduction for this growing population.
•Ultimately, EPA and the public need asurance that the most vulnerable segments of the population are being adequately protected from environmental contaminants.

Future Directions

•Continue characterizing susceptibility of the aging, and other life stages, against the standard young-adult reference group (with the Hamner Institutes through a cooperative agreement).
•Research on multiple life stages using cross-sectional designs will complement longitudinal studies on early exposures, development and aging.
•Longitudinal data are also required on human activity patterns for dose-rate estimates to improve EPA's time-series exposure models.
•Research combining multiple life stages will provide data that approximate the population, and will offer the first-ever quantitative estimates of population-level variance in sensitivity.

Contributors

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This poster does not necessarily reflect EPA policy.

Susceptible Populations