COMBINED STRESSES IN THE WORKPLACE
Report on the State of Knowledge

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October 1982
Final Report for period April-Oct, 1982
UNLIMITED DISTRIBUTION

Prepared for:
FLEET OCCUPATIONAL HEALTH OFFICE
NAVAL MEDICAL RESEARCH & DEVELOPMENT CMD.
NATIONAL NAVAL MEDICAL CENTER
BETHESDA MD. 20014

Office of Naval Research
Code 41
Arlington, Virginia

This document has been approved for public release and sale; its distribution is unlimited.
This contains about 375 analytic extracts from selected reports in world serial literature, on combined stress studies, in the laboratory and workplace, on humans and animals. Stressor pairs (physical or chemical) link sound, vibration, acceleration, heat & cold, ionizing & nonionizing radiation, with chemical solvents, drugs, dusts, gases, vapors, metals. Comments on limits in reported work & on response interactions (synergy, potentiation) are included.
SUMMARY

This report contains several hundred extracts prepared from selected reports on combined stress studies, in the workplace and the laboratory, on humans and animals. Stressor pairs of physical and chemical variables link sound, vibration, acceleration and impact, heat and cold, ionizing and non-ionizing radiation, chemical solvents, drugs, dusts, gases and vapors, metals etc. Brief comment is provided on the collective content of these papers as an image of this field, response interactions (synergistic, potentiating, additive, etc), and on limits and opportunities for further work. A supplemental set of key citations is provided.
PREFACE

This report has been prepared in accordance with format specified in MIL-STD-847A.

Acknowledgement is expressed for the material assistance of Mr. Buford Smith, of the NASA Technical Information Executive; Ms. Eleanor Goodchild of Univ of Penna Med Library; Ms. June Fulton of College of Physicians NLM Regional Medical Library; and Ms. Alice Makov of Thos Jefferson Med Library.
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Appendix A: Extracts of Combined Stress Reports
   Physical/Physical CS
   Chemical/Physical
   Metals CS
   Solvents CS
   Drugs CS
   Misc. Chemical CS
   Particles CS
   Gas/Vapor CS
   Epidemiology
   Surveys
   Supplemental Biblio I
   Supplemental Biblio II
1. INTRODUCTION

In most occupations, including those in the shipyard and on shipboard, the worker is exposed to a complex pattern of several stressor factors (e.g., heat, sound, chemical) which may or not be in ranges safe for sustained human exposure. Until recently, the reasonable route of study has been of one variable at a time, to extreme response in animals and to injury end point in human volunteers; and the practical way to select exposure tolerance limits has been to deal with the most critically dangerous factor. But there is an increasing, albeit still scarce reporting of controlled studies or good observations on events involving 2 or more stresses imposed simultaneously or in close succession. It was the task of this study to locate and examine a sampling of these reports, to select, collate, and extract their message, within quite limited effort constraints. Reports dealing with standards, measurement, protective and other design, case histories were generally left out. Communications from other disciplines doing studies on interactive factors (aerospace simulation, cocarcinogenesis and combined therapy, etc) were acquired incidental to the main searches, to examine their concepts.
2. OBJECTIVES

To survey and present an image of the state of knowledge on combined stresses, as observed and reported from the work environment or lab.

To screen and acquire an adequate sample of available world literature dealing with a variety of stresses in combination.

To extract salient information from each report, and to provide an extract and citation for each paper, in a standard and accepted format.

To comment on the recovered material, its scope and limits, and to recommend other efforts to acquire new data, elucidate mechanism, and develop standards and other information to benefit the program in Fleet Occupational Health.
3. METHODS OF APPROACH

Introduction

To guide the search and analyses on combined stresses, the outline below of detailed information sought was devised, as concept frame and check list:

Specific Stressor Variables $S_1, S_2, S_n$:
Dose rate and level, spectral band, modulation and waveform, vector direction, entry portal, total dose, treatment timeform.

Combined Stressors: pattern, treatment

Subjects: species, number, age: human operator, observer, subject, patient, passerby.

Tasks and their Standards

Environment of Exposure: workplace (the industry and task), lab, clinic, public place.

Modifiers: illness, medication, smoking, alcohol use, nutrition, fatigue, hydration, adaptation, etc.

Responses to single and combined $S$:
Biochemical, physiological, behavioral, pathological.
Criteria, measures, thresholds
Interactive responses measured and discussed.
Search and Acquisition of the Literature

Reports in the following disciplines and fields were examined:

**Occupational Health and Industrial Hygiene**
- Construction and shipbuilding
- Metalworking, foundry, smelting, plating
- Mining, mineral processing
- Chemical, petroleum, petroleum, plastics

**Public Health**
- Pollution ecology; air, water, soil
- Epidemiology

**Military, Naval, Aerospace Engineering & Technology**

**Clinical Medicine**
- Oncology: carcinogenesis, combined therapy
- Pathology, forensics
- Anesthesiology

**Sciences**
- Pharmacology and Toxicology
- Physiology: environmental, work
- Psychology: performance, work
- Nutrition
Search and Acquisition of the Literature

The sources used repeatedly or consulted include these:

**Local Libraries:**

College of Physicians: noted research library; used espec for foreign journals, monographs, NLM regional library services

Univ of Penna
Medical Library: one major working site for search/screen/recovery/copymaking
Applied Science Library: engineering journals, depository for certain documents eg NASA
Main (Van Pelt): other journals, reference services, foreign materials depository

Jefferson Medical Library: a major working site and complementary to Penn in its collection, esp occupat and environ hith

Franklin Institute Library: (Sci Museum & Res Ctr): the major site for acquiring Russian and other foreign journals, also strongest industrial chemistry collection

Drexel Univ Library: gov doc depository, complementing others used

Public Library Phila: major regional govdoc depository and indices; also multiple on-line services

**Federal Gov Doc Collections**

EPA Regional Ofc: Indices, reports, references
NIOSH Regional Ofc: indices, reports, references
OSHA Regional Ofce: reports, specialist consults

EPA Regional Ofc: Indices, reports, references
Energy regional ofc:
Nav Reg Med Ctr Library
HHS PHS Regional Ofc

**Special Data Bank Resources Used**

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- 8 -
Acquisition Strategy

Expected sparsity of papers determined the broadest multi-discipline and multisource screening search:
- First online screening used subject terms and suspected sites
- First library shelf screens, with a selected journal list
  (about 200) looking at current issues and latest annual index.
- Compilation of first citations found, and xerox capture of nominally suitable reports
- A convergent series of searches, with identification and revision of lists of productive authors, journals, sites, and topics
- Exclusion of hard to obtain communications (journals, reports, monographs, espec foreign) and of unproductive material
- Extraction of additional sources from biblios of recovered papers
- Special attention to surveys of combined stress titles
- "Forward tracking" through on-line bases for productive authors, through their moves and sources
- Exclusion of papers on measurement, design, cases, etc.

A file accumulates, becoming quite large, of citations and sources for further culling and search.

Acquisition is made more selective, and balanced with special effort to obtain samples of all desired topics

Specialized requests are prepared for searches, specific citationa and abstracts from the data services.

Selected foreign language materials are earmarked and acquired.

For the 1000 (approx) items in this report, about 50,000 papers were seen directly, and bases totalling over 10 mill were searched.

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Search Terms

To recover desired citations from several data banks used (NLM Medline, NASA Recon, NIH Grants, NIOSH, EPA, DTIC, NTIS) and the libraries, the concepts defining the field here must be redrafted in the language and search structural form for each system. In the limit, in some systems the wrong queries will get unsatisfactory or no responses. After preparing sets of terms for each system, these were merged into a composite which could be used (in part) for a number of search entries. About 100 terms comprise this set.
In laboratory experiments on the NADC Dynamic Flight Simulator, human subjects (4 trained 7 wks, in flight clothing) were exposed to: ACCELERATION, up to 1.03 Gz for 2.5 min, then patterned maneuver-like changes (ACM) of 3-5Gz for 10-20 sec, with return to 1.03 Gz for 2.5 min rest, repeated in 6 cycles in 160+ sec, with exposure pattern in each 1 hr repeated 6 times. Seat positions tried included 15, 30, or 60°; VIBRATION (V) buffet at 0.2 Gz peak, and 10 Hz, in the several seat back positions: SOUND (S), at 85 dba, frequency not given; HEAT, to 48-51°C; LIGHT LEVEL on instruments, 1 Lux or none. Tasks were: 2-axis tracking with RH side control and attitude/direction-indicator display; response time with peripheral light to be switched off. Two-five stresses were always present. In maneuver, there is increase in tracking error, response time, heart rate, fatigue, and no changes in bio-chem. Gz + buffet reduce tracking pfcme.
In laboratory experiments, human subjects (7 M ages 22-39 yr, fit) were exposed to: DEHYDRATION done by HEAT loading, to lose water, with Tcore kept at 30-38.5°C by immersion in bath at 41.5°C or air at 40°C, with Tcore then lowered to 22°C at rest for 60 min before next stressor, ACCELERATION, on AF SAM centrifuge, applied at two conditions: to subject wearing suit in capsule preheated to 38°C, or at 20°C. Two series of runs were made: "relaxed runs", with 2Gz for 1 min, then 3 Gz for 1 min, then rise at 1 Gz/sec to Gz limit; or "pressure runs", with 7 Gz for 1 min with activated anti-G suit and Valsalva maneuver (bearing down with closed glottis). Heat alone reduces G tolerance 0.4 Gz. Dehydration reduces G tolerance and yields an increased variability in responses to heat. Dehydration further enhances effect of G on heart rate increase and loss of blood vol, and interferes with anti-G reflexes, especially in rapid maneuvers.
PHYSICAL/PHYSICAL

COMBINED STRESS EXTRACTS
APPENDIX A

EXTRACTS OF SELECTED

COMBINED STRESS REPORTS
7. REFERENCE MATERIAL

| APPENDIX A  | EXTRACTS OF SELECTED COMBINED STRESS REPORTS |
| APPENDIX B  | SUPPLEMENTAL BIBLIOGRAPHY 1                 |
| APPENDIX C  | SUPPLEMENTAL BIBLIOGRAPHY 2                 |
6. RECOMMENDATIONS

The search and analysis on work in a number of special areas must be extended and expanded:

-for human studies, in the Western literature, for all variables, especially those for which animal work now dominates the scene, and for chemical/physical pairs in the workplace setting, in which the Soviet literature is largely represented.

-for animal studies, for all variables, for a number of species especially higher mammals, and for studies which try to link animal models quantitatively with human response for combined stresses.

-modulator factors work, where it is consciously designed in as a controlled part of a study; also data on limitations of work performance produced in various contexts by smoking, illness and fitness, prescription and OTC drugs, ethanol, nutrition, etc.

-examination of the work programs in combined stresses at about 100 presumed productive sites, and determination of "who knows and what" as well as obtaining current work images.

-examination of the report literature, by arranging for access and availability, including to restricted installations (this work can be further protected in analysis and publication); specific link to Navy programs.

-search for validation trial data (first from NIOSH and NIEHS) establishing kinds of criteria used for trial candidate selection, protocols, worksites and sponsors, Especially emphasize longer-term effects.

Evaluate ways to improve communications in the technology of combined stress studies: continuing surveillance over the field, possible newsletter, workshops and periodic meetings, sensitization of analysts at DTIC, NTIS, NLM including preparation of a CS thesaurus, participation in an occupational health clearinghouse, etc.
Generally, the journal articles selected here (peer reviewed and available anywhere) provided limited data to describe or verify statistic design or inference, dose conditions, or describe defensibly interactive response events or mechanisms. The report literature (from research contractors, Govt labs) when available, offers a freer and more copious range of information (albeit as good, if it derives from peer reviewed grants and nationally known labs). It may have much of the above desired information, plus data on method, speculations on mechanism, and discussions at length on problems—

No mechanism for exchanging information in this combined stress field exists. There is no formal communication between active sites, no continuing surveillance.
5. CONCLUSIONS

The journal disclosures on stressor pairs extracted here cover most of the combinations regarded as important (see matrix in this report).

There is an imbalance in the number of human studies reported in journals, compared with animal experiments, which dominate the literature. Little attempt is made to relate these combined stress data to human responses, except by dose-scaling and assumptions of additivity of known single variable responses.

Modulating factors are generally casually handled, except when they are formally part of the stressor set designed into the experiment. Nutrition, medication, drink, concurrent illness, smoking are modulators of main responses.

There is a pool of laboratory and study sites, which includes those from which the extracts have been drawn, and also a much larger group of presumably productive locales (up to 100 in U.S.). These have not been polled to learn of their activities on combined stress study.

There was no significant discussion in these experimental papers, of any rationale for modifying present exposure limit values rooted in single variable stressors, to accommodate data on interactive responses to combined stresses.

The work reported here (with a few self-evident exceptions) deals with research findings, which are considered only as suggestive until conclusively validated in some controlled study (counterpart of medical clinical trials).
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Figure 1. Stressor Pairs in Recovered Citations
Non-interactive events: independent, non-contingent, perhaps different sites, different modes of injury, interchangeable responses (2 insecticides, stomach or contact toxin).

Interactive events:
Additive, where there is parallel responsiveness, eg where dose-response regression lines are parallel, doses may be substituted, actions may be at the same target, summing of stimuli may be done algebraically additively.

Synergistic, supra-additive, 2+3=22, multiplicative, cooperative (Example: CCl₄ and/or ethanol in liver injury)

Antagonistic, infra-additive, 7+8=11, inhibitory, competitive, (eg anti-oxidant effects, Se & Hg). Functional antagonism, may be push-pull (eg barbiturates vs vasopressors); chemical (dithiopropanol BAL vs Pb or radiation); dispositional antagonism (competing at sites of absorption, metabolism)

Potentiation, one may have no effect but influences the other, 0+2=16 (isopropanol + CCl₄ effect on liver, etc)
4. RESULTS

Over 300 extracts of selected combined stress papers will be found in Appendix A, where they are grouped by major topics such as all-physical stresses, physical + chemical stresses, etc.

About 500 citations are displayed in the two supplementary bibliographies in Appendices B and C. For many, the papers have been hard to obtain (foreign sources or report literature with restricted access). Some are variants on papers already extracted in the set in App A. Nearly all are worthy of further analysis, requiring effort beyond the level afforded by this brief study.

Extent of coverage of possible combinations of stressor pairs is summarized in the matrix of stressor pair which follows. These combinations go beyond heat/noise/selected chemicals and were recovered incidental to the sweep of the main searches because of the possible insights into the data on interactive events.

About 80% of the reports describe animal studies, and 18% human studies. About 10 animal species are discussed. Many papers report on such modulating factors as smoking, nutrition, drugs, alcohol etc.

Response data, on events from biochemical through behavioral, for the single then combined stresses, generally do not refer to the fact of interaction, its measures, modes or mechanisms. Whether at the study's environmental level (physical interactions between particles such as dust/MgO and SO$_2$/NH$_3$/acrolein, or chemical, eg forming smog), or interactions at port of entry into organism or in its pharmacokinetic absorptions, transport, transformations, disposals; terms may be applied, casually, with local meaning only in that report (synergy, antagonism additive, etc). The definitively stated below, generally accepted, may be used in looking at these papers:
MODIFIERS cigs____alc____(O)sleep____drug(name)___________
diet_______age_______fit/ill__________other envir__________

ENVIRONMENT work(kind&task)__________________________lab__________
public vehicle______bldg______street______home__________

SUBJECTS anim(spec)____________human____ages____number____fitns____
optr/partcpt__subjct__patient__casual obsvr______________________

EXP DESIGN controls__________________stat param________________
epidem survy__________tol.stds(name/source)_____________________

RESPONSE DATA

System path(see list)_____________________________
Biochm/met path______________________________
Behavior/pfmce events_________________________
Respse Immed____Delayed______Acute______Chronic_________________
Tolerances Exceeded(MAC,TLV)____________________
Remarks________________________________________

COMBINED RESPONSE CONCLUSIONS,AUTHORS'

independent__________________additive_____________________
"synergistic"____________multiplicative____potentiated_________
antagonistic_____________competitive______compensatory_____
other non-linear_____bases for conclusions & mechanisms_________

QUALITY(1-3hi)adequ data_________adequ controls______________
rept relevance_________sound conclus_______________________
insight into combd__________QI(total,to 25)___________________
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<th>CHEM #1 Name</th>
<th>Phase</th>
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<th>Range, Steps</th>
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STRESS COMBINS: Names, Doses, Pattern (simul or consec)
Processing of Acquired Literature

Citations Handling

Control numbers were assigned to citations, reprints, and worksheets. Citations without reprints at hand were kept in a separate author file for search and dupe check.

Reprints Handling

A reprint is kept for every document analyzed, and in the groups reported here, eg physical, physical and chemical, particles....etc.

Analysis and Extraction

Stress pairs from each paper were entered into the matrix illustrated in this report, but kept here in more detail. A combined-stress analysis form (like the attached sample) and a worksheet accompanied each. Papers were screened again for relevance and quality, then an extract was prepared (containing salient data as available in the report on the stressor variables, subjects, environment, treatments, responses, data and comments on interactions. The final entries of extracts and citations were made on a modified version of the DD1473 form (now allowing full display of extract on face page), and removing clutter on classification, etc.) See Appendix A for these forms.
The Effects of Sustained Acceleration, Airframe Buffet, and Aircraft Flying Qualities on Tracking Performance

Piranian AG

USN Air Devel Ctr Warminster PA

1976

Aviat Space Environ Med
1976 (Apr); 47:458 (abstract)

In laboratory experiments on NADC centrifuge, human subjects (pilots) were exposed to: ACCELERATION to 5 Gz, sustained; VIBRATION, as buffet, to 0.5 Gz; and FLYING QUALITIES changes, with altered stability, maneuverability, controllability, responsiveness if simulated aircraft. Tracking tasks were scored for air-air miss distance, and % time within fixed radius of target. Pilots rated "flying qualities" as the dominant feature in tracking performance, but the presence of sustained Gz was significant in altering tracking performance. Buffeting Vibration Gz had negligible effect on performance.

acceleration, vibration, buffeting, flying qualities, combined stresses, tracking, pilotage, maneuver, interactive responses

Heat and Simulated High Altitude: Effects on Biochemical Indices of Stress and Performance

Francesconi RP, Fine BJ, Kobrick JL

Army Res Inst Environ Med Natick MA

1976

Aviat Space Environ Med 1976 (5);47:548-552

In laboratory experiments, human subjects (5 M 19-21 yr) were exposed to: HEAT, 35°C and 90% RH; HYPOBARIA, 4300 Meters. Treatments in a pattern of 7 hrs of continuous exposures, over 4 days, included: simulation of sea level hot wet climate, 35°C and 90% RH; and altitude, 4300 M and moderate temp, 22-23°C.

Tasks included: translating code, slide rule use, work with metro data. After 7 hrs exposure to heat, there were rises in plasma cortisol, dopamine-beta-hydroxylase, uric acid, with no effect on cAMP and cholesterol. After 7 hrs exposure to altitude, there were no changes in biochemical factors. Heat or altitude elicited different biochemical responses, but produced similar performance decrements. Heat + high altitude induce changes not seen with single stresses, in factors such as ACTH.

heat, hypobaria, combined stresses, biochemical indicators, task performance, plasma enzymes, hormones, interactive responses
In a field experiment in Nepal, human subjects (66 born at sea level and acclimatized 4 wk at 3800 M, and 24 Highlanders including 16 Sherpas born and raised at 3800 M) were exposed to: HYPOXIA (H) the pO2 present at altitude 3800 M (in a climate of moderate temperature and humidity), or HEAT (values not given) present with humid conditions at sea level.

In the hot humid sea level environment physical performance capacity was limited, and becomes as incapacitating as in the hypoxic environment at altitude. Both kinds of events are mediated through the cardiovascular system, with the degree of physical strain experience related to physical conditioning or acclimatization. Maximum heart and ventilation rates, and O2 uptake in the untrained may be reached at low work rates (eg in step test).
Cross-Adaptation in Military Trainees in a Hot Climate

In laboratory experiments and field observation, human subjects (military trainees) were exposed to: THERMAL STRESS, range from -10°C to +35°C ambient; HYPEROXIA, from 21%-100%. Treatments, considered against control data from trainees in summer and winter field scenarios, included: baseline exposure at 25°C for 4 hr; hyperoxia alone, 100% O₂ at 1 atmosphere; cold alone, -10°C to +15°C, with temperature pulsed in at start of hr 3 of 4 hr period, and last hr is recovery; heat alone with 10°C rises in pulse form to 35°C; 100% O₂ + cold, +15°C applied in pulse form; and 100% O₂ + heat, +35°C heat pulse. In heat adapted-trainees, basal metabolic rate falls; during acclimatization met rate first goes up. The heat-adapted show only limited physiological change. In the cold, heat adaptation leads to cross-adaptation. Hyperoxia augments adaptive change.

Key Words
- cold, heat, hyperoxia, physical training, acclimatization, cross-adaptation, interactive responses
This review discusses the multiple factors involved in the heat stroke syndrome. Topics include: modes of induction (active and passive); epidemiology; physiopathology and mechanisms (discussed as cases and findings), including malignant hyperthermia, dehydration, CNS changes (edema, irritability, cerebellar syndromes, coma), CV changes, hemostasis, proteinuria, GI symptoms (diarrhea, vomiting, jaundice), clinical heat cramps; also diagnostic methods; treatments and prevention (including rapid cooling, prophylactic antibiotics, rest, hydration).

**KEYWORDS**
heat stroke, combined stresses, hot climates, hyperthermia, dehydration, interactive responses
In laboratory experiments, minipigs (4, cold acclimatized) were exposed to: COLD (C), at 7°C for 2 hr, or 25°C for 30 min; HYPOXIA (H), with 10% O₂ in N₂ total sea level pressure; and NOREPINEPHRINE Bitartrate (N), 2 µg/kg/min iv for 20 min. Treatments involved various combinations of these. Hypoxia reduced metabolic responses to cold in sensitive species, due to effects on heat production mechanisms (non-shivering thermogenesis). 

N increased O₂ consumption and rectal temperature in normoxic but not hypoxic animals. Cold also increases O₂ consumption in normoxic and hypoxic animals.
**Thermogenic Processes during Cold in Hypoxia**

In laboratory experiments, dogs (31 mongrel, adult, postabsorptive, unanesthetized) were exposed to: COLD (C) at 60°C or 26°C; HYPOXIA with 12% O₂ in N₂ at sea level pressure (O); or HORMONES (H) epinephrine or norepinephrine 2 ug/kg/min iv 10 min. Treatment included: T6 3 hrs; T6 + O₂-12; or T6 + O₂-12 or H(Ep); all in various combinations. Low temperature alone increased (sustained) O₂ consumption, rectal temp., glucose, FFA. Low temp. + hypoxia did not change oxygen consumption, abolished rises in Trect which kept falling, and there was no change in FFA, glucose. Hypoxia induced a decrease in body heat content, after reduced heat production and initially reduced O₂ consumption (which rose after 50 min to pre-hypoxic values). Hypoxia reduced cold-induced increase in O₂ consumption. With H (ep) infusion, O₂ use rose over 15 min period; norep caused a similar rise. O + H (ep) smaller O₂ use rise than ep alone, back in 15 min.
**Extract**

In laboratory experiments, rats (24 M) in metabolic chamber, were exposed to: COLD at 50°C; HYPOXIA, with 14% oxygen in nitrogen at normal pressure. Treatments included: 14% O₂; 5°C; O₂(14)+T(5); with 30 day exposures. At a given water intake, all test groups produced more urine than controls. Cold + hypoxia do not show a summation of responses produced by each, for serum osmolality, post-environment drinking, water intake and urine output. Cold + hypoxia can increase metabolic rate, at a reduced response compared with cold alone. Speculations consider a complex endocrine interaction. But at 28 day when pitressin was used to test concentrating ability of the kidney, this failed to have an effect in reducing urine output in cold or cold-hypoxia treated animals.

**Keywords**
cold, hypoxia, combined stresses, water balance, diuresis, kidney concentrating ability
Cross-Adaptive Effects of Cold, Hypoxia, or Physical Training on Decompression Sickness in Mice

In laboratory experiments, mice (M. swiss) were exposed in 2 studies to: COLD (C) to 4°C continuously; HYPOBARIA AND HYPOXIA (P) at 379 Torr (0.5 atmo); and HYPERBARIA (H) to 7.6, 8.8, 9.9, and 11.1 ATA. In one treatment of 28 days: T4 for 4 hr; then P4 for 4 hr; then treadmill exercise 2 25-min sessions with 5 min rest; then swim for 15 min at 31°C. On day 28 subjects were exposed for 24 hr in decompression chamber in various sessions to H 7.6-11.1 ATA for 30 min, then rapidly decompressed to 1 ATA. Survivors were counted after 30 min. Treatment 2 (14 days): P4 for 4 hr; treadmill 3 25 min sessions, with 5 min rests; compression to 1.3 ATA with P02 of 0.5 ATA, then H at 1.8 atmo/m to desired peak ATA, held 30 min, then decompressed to 1 atmo. Decomp. tolerance is not affected by cold exposure or swimming. Treadmill raised decomp tol.; P reduced tol. to decomp.
**Effect of Breathing High Oxygen Mixtures on Metabolism during Shivering**

In laboratory experiments (limited data are provided), human subjects were exposed to: COLD in chamber; and HYPEROXIA. With cold, shivering was not necessary for metabolic rate increase, although it augmented metabolic rate. Cold and hypoxia inhibit shivering, but metabolic rate is up as much as 14% here. A variety of combined effects are suggested.

**Key Words**
cold, hyperoxia, combined stresses, shivering, thermogenesis, metabolism, interactive responses
In laboratory experiments, human subjects (10) were exposed to: COLD, at 10\(^{\circ}\) C and 25\(^{\circ}\) C; and HYPEROXIA, at 100\%. Oxygen alone vs air showed no change in O\(_2\) consumption. At low T, when on O\(_2\), a decrease in O\(_2\) consumption occurs (to 30\% of the increase in O\(_2\) consumption in the cold). There is also lowered heart rate, respiratory frequency, minute volume, EMG. It is speculated that this drop in O\(_2\) relative to air may be a central reflex event, since the normal response to cold would include an increase in O\(_2\) use, respiratory rate, etc).
**REPORT DOCUMENTATION PAGE**

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**EXTRACT**

In laboratory experiments, human subjects (11 M 23-26 yr, healthy) were exposed nude to: HYPEROXIA (O) at 100% via mouthpiece; and COLD (C) or HEAT (H), at 22.4-26.5°C or 36.6-39.3°C. Tests were made of cold threshold 30 min after breathing O2 with exposure of a 50 cm² chest area to a dry ice shutterbox radiant stimulus. At warm ambient T, any O2 effect on threshold is independent of that reflex vasoconstriction which would be found in a cool environment. O2 inhalation raises perceptual threshold for cutaneous cooling. Cool environments raise threshold. O2 inhalation elevates tissue pO2, reduces chemoreceptor tonic activity, and may alter the essential chemical metabolic nature of the cold sensing system.

**KEY WORDS**

hyperoxia, heat, cold, combined stresses, thermoreceptors, cold sensing, neural thresholds, interactive responses

**NOTES**
The Effect of Breathing 15%, 21%, and 100% Oxygen on the Shivering Response of Nude Human Subjects at 10°C.

In laboratory experiments, human subjects (6 M) were exposed to: COLD, at 10°C up to 90 min; and OXYGEN (O), at 15, 21, 100%. Measurements were made of ventilation, oxygen, shivering. Response is very variable: degree of shivering goes up with time of exposure. The times to onset, then to severe shivering due to cold are increased by higher PO2.
**Human Cardioaccelerative Responses to Hypoxia in Combination with Heat**

In laboratory experiments, human subjects were exposed to: HYPOBARIA and HYPOXIA in ascents to 18,000 ft in chamber; and HEAT to 49°C. One Group (19 M, 25-30 yr) were decompressed in a heated chamber: T 49°C for 15 min, then ascent at 6000 ft/min to 18,000 ft, staying for 12 min. Group 2, exposed to hypoxia later than heat, (5 M 30-45 yr) were heated to 49°C for 15 min, then exposed to O₂-N₂ mix with pO₂ of 75 mm Hg (like 18,000 ft) but with total pressure at sea level. Exposures were to heat or heat + hypoxia or hypoxia 15 min after start of heat. Group 3 were exposed to hypoxia equivalent to 14,000 ft + 49°C heat; and Group 4 were given hypoxic exposure + heat together for 45 min. 12/19 subjects decompressed to 18,000 ft without extra O₂ had induced greater heart rate compensation in heat. In 7/19, the heat is antagonistic, blocking changes in heart rate from hypoxia. Heat before/with hypoxia induces bradycardia, loss of vasc.tone.

**Key Words**
hypobaria, hypoxia, heat, decompression, combined stresses, bradycardia interactive responses
 Effect on Rate of Exposure to Heat and Vibration

In laboratory experiments, rate (200 M adult SD), in cages in environment chamber, were exposed to: VIBRATION, 17.5 G rms overall, flat from 100-500 Hz, with droops to 5 Hz and 800 Hz, direction not given but may be transverse in restrained subjects; also HEAT, with temps over range 26.7°C-46.1°C for 20 min; and treatments in various patterns of single or combined exposure. V increased hemoglobin, hematocrit, SGOT (20 min post exposure). This may be due to shift of fluid to extravascular spaces. H alone gave no changes in Hb, Ht, SGOT, at 20 min post exposure. V + H caused further increase (beyond V alone) in Hb, Ht, SGOT (at 20 min; 24 hrs later returns to normal); increased organ wts (heart, kidney, adrenal); and mortality at 2 hr post exposure to V + H is much greater than each acting separately. Synergies here may be best observed when single stressors are set close to lethal levels.

heat, vibration, combined stresses, blood volume, fluid balance, pathology, interactive responses
In laboratory experiments, rats (130+ M adult SD) in cages in environment chamber, were exposed to: VIBRATION, 17.5 G rms overall, flat from 100-500 Hz, with droops to 5 Hz and 800 Hz, direction not given but may be transverse in restrained subjects; also, in another experimental condition, VIBRATION at 15 G peak at 60 Hz sine, random direction; or HYPOBARIA, at 0,5000, 7500, 10,000, 14,000, and 18,000 ft. Treatments were: V60 + all altitude conditions; or V60 with 18,000 ft but 100% O2 at sea level equiv; or Vrandom alone. No changes were seen due to V at sea level or V + P until 10,000 ft, then V tolerance dropped as function of altitude. At 14,000 and 18,000 ft mortality is increased. V + P (high alt but sea level O2) has no effect, reduced pO2 is the primary altitude factor. Vrand + P at 18,000 ft more deaths than V or P at 18,000 ft alone. V weakens lung structure, and contributes to death synergy: P 5%, V 8%, P + V 80%.

19. KEYWORDS
vibration, hypobaria, hypoxia, combined stresses, altitude tolerance, interactive responses

20. NOTES
In laboratory experiments, mice (153 M 32 wks, CFE) were exposed to: VIBRATION, 7.07 G rms, 20 Hz from shaker, for 10 min, with direction not given; and POSITIVE PRESSURE BREATHING (PPB) at 1.5-6.0" H2O into mask, as separate or combined stresses. V usually causes 70% mortality, with lung atelectases. V + PPB at eg 3.75" H2O yields scattered petechiae, but subjects otherwise normal. (Note that V max effects of thoracico-abdominal resonance at 4-8 Hz are not involved here). PPB protects lungs, etc. by reducing amplitude and intensity of pulmonary distortion. One can equate the V forces with the PPB compensatory forces.
An occupational health study found forestry workers (711 M incl 142 chain saw users) exposed to: VIBRATION, chain saw amplitudes over 80 micron (local allowable level), with major frequency of 125 Hz, and transfer through trigger handle orthogonal to chain bar. Exposures were 4-6 hr/day up to 10-12 yr. Concurrent exposure to COLD and SMOKING were considered, and questionnaire was used. Vibration syndrome (VS) damage to hands included blanched fingers, sensory loss, tremors, osteoporosis, joint cystic changes. VS prevalence in chain users was 44%, non-users 18%, function of length of exposure, and regionally different (high S. England, low in Scotland). 90% with VS had worked 10-12 yr. VS was affected by cold stress (chilling at work, travel), which may trigger established VS to produce symptoms, worse in winter. Smoking intensifies the effect and numbers in the VS groups.

**Keywords:** vibration, cold, combined stresses, vibration syndrome, chain saws, vibrating tools, forestry, white finger, Reynaud's disease, sensory pathology, cardiovascular pathology, smoking, interactive responses
Occupational health observations in a limited descriptive report, are provided about workers (165) in reinforced concrete and construction, in two groups: 1. Healthy, with normal immune system, and 2. Those with ALTERED IMMUNE STATE: allergies, increased cholinesterase activity, sinus arrhythmias, aspermia gynecological disorders, most attributed to reduced immune reactivity. These groups had occupational exposures to: VIBRATION, of 0.01-0.6 mm (and 0.11-10.0 cm/sec) at 5 Hz, with no other information, but probably from vibrating tools. Measurements were made of serum lysozymes and complement, passive hemagglutination reactions (eg tetanus and diphtheria antibodies), rbc latex sedimentation, etc. The signs of vibration syndrome were worse in those with immune deficiencies, as well as in those with aspermia, gynecological disturbances, cardiovascular and neurological deficiencies.

**Key Words**
- vibration
- immune deficiencies
- combined stresses
- construction industry
- vibration syndrome
- allergy
- aspermia
- gynecological disorders
- interactive responses
Occupational health observations of a limited descriptive nature are provided for workers (44 M, 86 F, 18-60 yr) in Naval shipyard jobs, in welding, painting, assembly. These combined stressor variables were examined: VIBRATION; SOUND (90-112 dBA of broad band noise); CHEMICALS, including Zn, Ti, Pb, also dyes and stains; DUST; FORCE and WEIGHT LOADS. Vibration sensitivities were impaired as a function of occupational exposure. In studies with a "vibrotester" at 63, 125, 250 Hz, impairment losses involved drops over 25 db. There were early findings of polyneuritis. No other data are given.

**Key Words**
- vibration, sound, chemical toxics, dust, combined stresses, welding, painting, shipbuilding, metals, dyes, polyneuritis, touch sense, pressure sense, interactive responses
In laboratory experiments, human subjects (8 M 21-29 yr, fit) were exposed to: DEHYDRATION with HEAT at 125°C 20-30% RH in chamber exposures for 2 hrs; and ACCELERATION, with onset and decay rates of 0.3 Gz/sec, and peak Gz held for 15 sec. First runs were peaked at 3.0 Gz, and 0.2 Gz increments for each run to blackout (with loss both of central and peripheral vision). Treatments were: Gz alone (with subjects); or non-experimental (controls) at room temp, given water ad lib, then Gz runs; or subjects in hot chamber 2 hr, down to room temp for 10 min, then 1 hr rest, then Gz. In another series, subjects in chamber with bouillion and water, then Gz; or lunch & water, then Gz. Gz + Dehyd (loss of 1-3% body wt) dropped Gz tol. (4.9 down to 3.5 Gz), as function of temp. Gz tol. was not lost if heated and hydrated. Related to changes in retinal blood flow and water balance.
In laboratory experiments, human subjects (6 19-36 yr, fit) were exposed to: ACCELERATION on centrifuge, Gz raised at 1 Gz/sec and held 15 sec at grayout threshold; HEAT and COLD pre-conditioning in this pattern: water immersion to reach 38.5°C core temp; immersion to 37.8°C core temp; normal core temp + skin vasodilation by using warm surface air; normal core temp and normal surface air; normal core temp + skin vasoconstriction by using cold surface air. The core temps were stabilized during G runs by wearing ventilation harness. It was found that one normal endpoint of 3.2 Gz dropped 0.9G at 38.5°C CT, dropped 0.5 Gz at 37.8°C CT, and fell 0.3 Gz at normal CT with skin vasodilation. The interactive additive effect is on the CV system.


1. REPORT NUMBER

2. GOVT ACCESSION NO.

3. CATALOG NUMBER

A0275

4. TITLE (and Subtitle)

The Effect of Hypoxia on Tolerance to Positive Acceleration

5. TYPE OF REPORT & PERIOD COVERED

Jnl article

6. PERFORMING ORG. REPORT NUMBER

NADC-MA-5905

7. AUTHOR(s)

Burgess BF Jr

8. CONTRACT OR GRANT NUMBER(s)


9. PERFORMING ORGANIZATION NAME AND ADDRESS

USN Air Dev Ctr, Av Med Accel Lab, Johnsville PA

10. PROGRAMELEMENT, PROJECT, TASK AREA & WORKUNIT NUMBERS

11. CONTROLLING OFFICE NAME AND ADDRESS

12. REPORT DATE

1958

13. NUMBER OF PAGES AND REFS

4P no R

14. PUBLICATION

Aerosp Med 1958 (10); 29:754-757

15. EXTRACTION

In laboratory experiments, human subjects (4, trained) were exposed to: HYPOBARIA and HYPOXIA, in mixed conditions, with altitude of 16,000-21,000 ft, and oxygen at 9.5, 10, 10.5, 11.0, 11.5, and 21.0%; and ACCELERATION, in 0.25 Gz increments, from 2.5 Gz in 12.5 sec to max Gz, held for 15 sec, with end point peripheral light loss. Treatments included 4 sessions for each of the oxygen mixes and various altitudes with centrifuge runs from 2.5 Gz to PLL over 3 min total. Gz + hypoxia reduced tolerance 0.7-1.0 Gz, also with big changes in respiration, and dulling of perception. There was occasional simultaneous central vision loss in 50% of subject runs at 4.5% and 10% oxygen. A wide variability in response was shown.

16. KEY WORDS

acceleration, hypobaria, hypoxia, combined stresses, altitude, grayout, interactive responses

17. NOTES

DD FORM 1 JAN 72 1473 (MOD)
# The Effects of Time and Temperature upon Tolerance to Positive Acceleration

**ABSTRACT**

In laboratory experiments, human subjects (30 M trained) were exposed to: HEAT and COLD, from 150°C to 55°C air; or ACCELERATION, in range 1-5 Gz for 30 sec, 1 min, 2 min; unprotected or wearing anti-G suit (G4A). End point of tolerance was peripheral light loss. With G alone, applied to PLL end point, condition lasts about 6 sec, then reflexes provide recovery and a gain of 0.5 Gz more tolerance. Gz tolerance is reduced at 25°C (where there is cold, shivering). Gz tolerance is also reduced at 37°C (where subjects appear hot and sweating) but only 0.5 Gz less than effects of Gz + cold.

**KEY WORDS**

acceleration, heat, cold, combined stresses, grayout, anti-G suit, interactive responses
In laboratory experiments, human subjects (4 M 21-23 yr, fit) were exposed to: VIBRATION at ± 0.4 Gz, over range 2.5-20 Hz sine, in 0.5 Hz increments, coupled into "semi-supine" seat; or ACCELERATION at 1, 2.5, 4.0 Gz, to "semi-supine" seat. No other data given. Mechanical impedance (magnitude and phase components) to vibration was measured. At accel. of 2.5 Gz vibration resonances were seen in range 9.5-12.5 Hz. Stomach vibration begins at 9.5 Hz and continues to 11.5 Hz. At 7, 11, 18 Hz pain and lowered tolerance to vibration is found. The Gz biases body dynamics, causing increased stiffness and high energy transmission to internal organs.
**Title:** Effects of Hypohydration on Work Performance and Tolerance to +Gz Acceleration in Man

**Authors:** Greenleaf JE, Matter M Jr, Bosco JS, Douglas LG, Averkin EG

**Performing Organization:** NASA, Ames Res Ctr, Biotech Div, Moffett Field CA

**Publication:** Aerosp Med 1966 (Jan);37:34-39

**Excerpt:**

In laboratory experiments, human subjects (9 M 21-29 yr) were exposed to: HYPOHYDRATION, with water reduction in 3 series; in wk 1 subjects given 1500 cc/day, in wk 2 ad lib water, in wk 3 900 cc/day, then on test day6 given 200 cc water, 1 gm NaCl, and sustagen nutrient; also ACCELERATION on Ames 5. degree of freedom centrifuge at 3 Gz/min to grayout (usually about 5 Gz), with 3 runs and 1.5 min between runs. Other tests of water tolerance were: motor treadmill, Harvard step test, isometric muscle strength, and blood chem, hematol, cardiovascular and neural measurements. Hypohydration to 4% made no change in tolerance to Gz, some exercise tests. If H is over 4%, there is loss of Gz tolerance, if H is 4-4.5% deterioration in step test, and change in O2 use. Well conditioned subjects show no changes in 4-5 days; they may draw on a body pool of free circulating water (FCW).

**Keywords:** hypohydration, acceleration, exercise, combined stresses, water balance, grayout, blood volume, interactive responses
In laboratory experiments, human subjects (16 M 18-24 yr) were exposed to: ACCELERATION, in rapid-onset-runs (ROR) at 1 Gz/sec holding for 15 sec at peak tolerable Gz, or in gradual-onset-runs (GOR) with rise at 1 Gz/15 sec. End point was peripheral light loss; and SODIUM intake control, to levels of 10,50,100,150 mEq/24 hr, with K held at 100 mEq/24 hr and water to 2000 cc/24 hr and enough calories to maintain wt. With sodium reductions, plasma volume is reduced from 0-23%; Gz tolerance (ROR) drops 0.2-0.7 Gz and (GOR) 0.2-1.35 Gz, for all levels of sodium intake (10-150 mEq/24 h). There are large effects caused by small negative sodium and water balance changes; and even when baroceptor reflexes have time to act with GOR, these can't hold cerebral blood flow at suitable levels.

**Key Words**
acceleration, hyponatremia, combined stresses, blood volume, grayout, sodium deprivation, blood flow, interactive responses
**Extract**

In laboratory experiments, human subjects (6) were exposed to: HEAT, 750°F (at 55% RH uncontrolled) to 160°F (90% RH) in pre-heated gondola for 20 min before G runs; and ACCELERATION, with rise to 2Gz, then up in 0.2 Gz steps until peripheral light loss. Peak Gz was reached in 7 sec, held at 15 sec, with final run in each series 4 min at 0.25 Gz below grayout. Repeat runs, with 3 min rest periods took 1 hr in gondola each series; there were 8 rides each at selected heat, daily, over 3 wk period. Heat reduced tolerance to Gz, without changes in response times per se until limit of heat exhaustion or poor coordination was reached. The lowest temp. to degrade Gz tolerance (by 0.2 Gz) was 100°F. For temp. alone, upper limit was 160°F, where skin temp was 102°F (and nausea, double vision, tachycardia at 170 beats/min occurred); here, a 1 Gz reduction in tolerance was found.

**Key Words**

Acceleration, heat, combined stresses, centrifuge, grayout, heat exhaustion, interactive responses

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In laboratory experiments, dogs (12 M/F, 10-15 Kg, unanesthetized) were exposed to COLD (C) at 60°C and 260°C and HYPOXIA (H), 12%. Treatments were: C26 30 min with room air; C6 60 min with room air; C6 + H12. There is a hypoxic reduction of the thermogenic response to cold; the increase in O2 use induced by cold in air is suppressed immediately by hypoxia, and gradually recovers with shivering. H causes no change in plasma glucose, lactate, pyruvate FFA and ketones. Cold induces rise on FFA and ketones earlier in hypoxia than air; with limited O2 to tissue, and ATP genesis reduced, FA oxidation is reduced and glucose accelerated. The reduced metabolic response to cold in hypoxia relates to impaired capacity to accelerate substrate oxidation rather than reduced substrate mobilization. Hypoxia suppress part of the non-shivering thermogenesis component.
Altitude and Hypoxia as Phase Shift Inducers

In laboratory experiments, human subjects (1F, 2M, 19-21 yr) were exposed in chamber simulation to: HYPOBARIA, to altitude of 25,000 ft for 30 min, with oxygen mask in place; starting with 30 min of denitrogenation, then to 5000 ft in 1 min, return to ground level, ascent at 5000 ft/min to 25,000 ft. Now, mask was removed for 3 min to induce hypoxia, then descent at 5000/min to ground. Diurnal rhythms were found as reference in 24 plots of measured T oral, peak expir flow, grip strength, calculation and recognition tests. After exposure to combined stresses, shift in phase occurred concurrently in rhythms of several factors, induced immediately after exposure, maintained for 4 days, then in incoherent ensemble reversed its shift. The report discusses possible oscillators and synchronizers in organisms.

diurnal rhythms, altitude, hypoxia, combined stresses, rhythm phase shifts, internal oscillators, body temperature, hypobaria, interactive responses
This discusses field observations made on winter 1967 ascent of Mt. McKinley (20,320 ft). This included initially 8 climbers, ages 23-39 yrs; 3 reached the summit. Exposures included: COLD to -42°F; HYPOXIA AND HYPOBARIA to 20,320 ft; WIND, causing chill and dehydration (data not given). Schedule was: 10 days from 1500-14,400 ft, several days acclimatizing at 17,300 ft, 1 day to 19,000 ft, 1 day to summit at 20,320 ft, 7 days down to 18,200 ft, then 1 day down to base. No other data are given. They report observing extensive physiological change beyond acclimatization: dehydration, exhaustion, weight loss, lassitude, LDH and CPK 2-5X normal (espec in cold injury), postural balance deterioration.

**Key Words**
cold, hypoxia, combined stresses, mountaineering, Mt. McKinley, high altitude, wind chill, dehydration, fatigue, acclimatization, tissue enzymes, interactive responses
Effects of Lowered Body Temperature on Hyperoxic Seizures

Giretti ML, Rucci FS, LaRocca M

ITALY: Univ Sassari, Sardinia
Instit Human Physiol, Instit Clin Surg


In laboratory experiments, rats (90 SD) were anesthetized, then implanted with electrodes into frontal cortex dura, and thalamus. They were exposed to: COLD, to selected 15–35°C rectal temperature endpoint in 3–8 hr; and to HYPEROXIA (O) to 5 ATA in hyperbaric chamber. Hypothermia reduces electrical activity of cerebral cortex (at 21–25°C there are pre-epileptic spikes seen) but generally hypothermia in 15–35°C range stops appearance of hyperoxic seizures; and at 27–31°C the incidence and latency are reported to be like normals.

**Key Words**
hyeroxia, cold, combined stresses, hyperbaria, hypothermia, seizures, neurologic syndromes, interactive responses
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<td>J Appl Physiol 1961 (1);16:1-7</td>
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<td>In laboratory experiments, mice (379) were exposed to: HYPEROXIA ((O)) at 1-11 atmo.; and CARBON DIOXIDE ((CO_2)), 0-304 mm Hg in 38 combinations for 90 min periods. Endpoints were convulsions (first seizures) and death. (O) is convulsigenic over 3 atmo, and lethal over 4 atmo. (CO_2) at various conc in 1 atmo of (O) is not convulsigenic, but is lethal at high (pCO_2). In (O) high pressure ((OHP)) addition of (CO_2) shortens survival time, and small rises of (CO_2) shorten preconvulsive periods, and is (pCO_2) is over 120 mm, convulsions are inhibited. (CO_2) decreases tolerance to high (pO_2), and high (pO_2) increases toxicity of high (pCO_2). Low (pCO_2) increases resistance to electroshock, but decreases resistance to OHP convulsions, an event reversed at (pCO_2) in range 90-120 mm Hg. These are potentiation relations of (OHP) and (pCO_2).</td>
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<td>In laboratory experiments, rats (820 F albino) were exposed to: HYPERBARIA (P), to 10, 25, 40 ATA; HYPEROXIA (O) to 4.2 ATA; in 42 experimental conditions, with temperature held at 28⁰ C. When O was raised to 4.2 ATA during P to 40 ATA, decompression was erratic, and O toxicity signs were found in CNS. There appears to be an increased sensitivity to O in He at raised pressures. An O envelope is defined as the range of elevated pO₂ usable to aid decompression; and optimum O level and envelope size depends on ambient P &amp; exposure time. At short shallow exposures, optimal O level is high. If O is too low, decompression sickness may occur, and if O is too high for the conditions, O toxicity may result.</td>
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This brief survey discusses properties of oxygen which contribute to its toxicity in some conditions. A variety of dangerous reactive intermediates may be produced, in certain "minority pathways" of reaction (about 5% of total events). These may include, eg.: $O_2^-$ superoxide, $H_2O_2$, OH hydroxyl radical. These may be produced under ordinary conditions in respiring cells. Defenses include superoxide dismutases, in all cells, which scavenge $O_2^-$, yielding hydrogen peroxide (which catalases and peroxidases may deal with) and $O_2$. In phagocytosis, in which bacteria can be engulfed without need for $O_2$ but can't kill unless $O_2$ is present, active intermediates may be produced, and these may be increased under hypoxia. After hypoxic events, damage may occur (eg in cerebrovascular problems) when normal reoxygenation is established and these substances accumulate.

**KEY WORDS**
- hypoxia
- oxygen toxicity
- reactive intermediates
- superoxides
- hydroxyl radical
- dismutases
- phagocytosis
- minority pathways
In laboratory experiments, rats (NMRI-SD derived), mice (M NMRI), and guinea pigs (M Hartley) were exposed to: HYPERBARIA (P) at 25, 50, 75, 100 psig; CARBON MONOXIDE (CO) to 6350 ppm, different levels for the various species; with oxygen maintained 140-160 mm by adjusting mix, in 4 hr study, with stepwise increases in P, then decompression with 79% He and 21% O₂. In animals that died, the COHb levels and LC₅₀ values as function of pressure were set down. All animals were unconscious during hrs 1 and 2 with CO. There was no change in toxicity of CO in these species as total P increased up to 100 psig. The equilibrium % of COHb produced by a conc of CO was independent of environmental P.

**Key Words**
- carbon monoxide, hyperbaria, combined stresses, oxygen, toxicity, carboxyhemoglobin, interactive responses
Physiological Responses of Men Working in 25.5°C Water, Breathing Air or Helium Tri-mix

In laboratory experiments, human subjects (M, av age 34 yr, divers and diving officers) were exposed to: THERMAL STRESS, 25.5°C water immersion; and GAS MIXES; 35% He + 21% O₂ + 43% N₂ (trimix) at 3 M depth. Treatment sequence was: Water immersion, breathing air day 1, then either air or trimix day 2, with day order reversed for ½ the subjects. EXERCISE WORK was done, on ergometer, with 3 cycles of immersed work, 4 mins of rest, 6 min of work, then 4 min recovery cycles. Cold reduced Trect despite exercise, and contributed to increased O₂ use and catecholamine excretion. Immersion caused a skin vasoconstriction, and work and scuba breathing added to a brisk diuresis (with centralizing blood vol). Trimix yielded higher minute ventilation, but lower O₂ use than air. Trimix scuba breathing yielded a smaller diuresis. The fall in core temp during work in water was the same for air and trimix. Work and cold stress responses are modified by the trimix.

helium gas mixes, cold, exercise, combined stresses, trimix, catecholamines, diuresis, scuba breathing, body temperature, oxygen consumption, interactive responses
### Extract

In laboratory experiments with mice, they were exposed to hyperbaria with helium, up to 183 ATA, to study the effects on the potency of anesthetics, including: N\(_2\)O, CF\(_4\), SF\(_6\), N\(_2\), Ar, CC\(_4\), hexafluoroethane, at various pressures and doses. Of interest was the ED\(_{50}\) where the beginnings of high pressure neurological syndrome would occur. Various signs: spasms, rhythmic tension and relaxation, altered righting reflexes were seen for different doses of N\(_2\)O, N\(_2\), Ar, CF\(_4\). Pressure increased the ED\(_{50}\) for loss of righting reflexes by 36% at 100 ATA for most of these. Subanesthetic partial pressures of all the gases raised the ED\(_{50}\) pressure for spasms. It is suggested that 2 mechanisms apply: anesthetics work by expanding some hydrophobic phase critically, and hyperexcitability occurs when pressure reduces the volume of some hydrophobic phase by a critical amount.

### Keywords

hyperbaria, anesthetics, combined stresses, nitrous oxide, carbon tetrafluoride, argon, nitrogen, sulfur hexafluoride, helium, high pressure neurological syndrome, critical volume hypothesis anesthesia.
In laboratory experiments, mice (over 100 M swiss albino, age 2 mo) first kept in chamber at 33°C, were exposed to: SOUND, of 100, 105, 110 dBa at 50 Hz sine; also 60, 80, 100 dBa at 500, 2500, 10,000 Hz sine, all for 2 hrs, from loudspeaker; then EXERCISE, "swimming time" after drop into pool with 1.2-2.0 gm weight on tail, then "time to submersion". This time to submersion was reduced at sound of 80 or 100 dBa 500-10,000 Hz, also with sound over 100 dBa at 50 Hz. Seizures occurred within first 10 min of swimming; other signs of CNS excitation increased with both sound frequency and intensity. Muscular exhaustion was associated only with sound intensity, not frequency.

**Key Words:**
- sound, exercise, combined stresses, neural disorders, survival, convulsions, interactive responses
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<td>In laboratory experiments, mice (200 M swiss albino), first kept in chamber at 33° C were exposed to: SOUND, at 60, 80, 100, 105, and 115 dbA at 50, 500, 2500, and 10,000 Hz for 60, 90, 120 min, from a loudspeaker; then EXERCISE, &quot;swimming time&quot; after drop into pool with weight on tail, to time of submersion. Time to submersion is reduced at 80 and 100 dbA for frequencies of 500,2500,10,000 Hz; higher levels are needed at 50 Hz. Convulsive crises of 3-6 sec duration appear within first 10 min of swimming, eg with 100 dbA at 2500 and 10,000 Hz; from some increased excitation of the CNS.</td>
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In laboratory experiments, human subjects (M, young, 9 groups) were exposed to: HYPOXIA, PO2 12% in N2 sea level pressure; and HEAT, 50°C. Treatments, after pre-exposure and room air and temperature controls, included: 12% O2 for 2,15,45 min; heat at 50°C for 15,45 min; 12% O2 + heat 50°C for 15,45 min. Measurements included: Tskin, Trect, cardiovascular and respiratory indices, ACTH, adrenocorticosteroids. Cardiovascular responses to hypoxia were intensified by heat. There were no consistent changes in blood adrenocorticoids. No other data are available.

hypoxia, heat, combined stresses, physiological performance, endocrine, cardiovascular system, thermoregulation, interactive responses
This review discusses a variety of factors involved in the action of microwaves and RF radiation. Frequency ranges considered are 300 KHz to 300 MHz RF and 300 MHz-300 GHz. Topics include: thermal vs non-thermal effects, experimental studies on cell, tissue, and organism chemistry, growth, endocrines, immune system, nervous system, behavioral effects; also extrapolation from animal experiments to man and utility of animal models. Surveys of human exposures, epidemiology of this radiation, critiques of Eastern European reports are discussed, and protection guides and standards, product emission and exposure standards are considered.

**KEYWORDS**

microwave radiation, radio radiation, multiple stresses, radiosensitivity, radiation pathology, non-thermal effects, non-ionizing radiation standards for protection
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**T tolerate of rats to a cold environment during multiple exposures to a low dose of X-rays**

**KEY WORDS**
- x-radiation
- cold
- combined stresses
- divided dosages
- radiosensitivity
- undernutrition
- tolerance
- interactive responses

**EXTRACT**

In laboratory experiments, rats (N, SD) were exposed to X-RADIATION (X) at 25 R/min, total 600 R, 250 kvp, whole body; and COLD, 6°C and 23°C. Using lethal doses made sublethal by fractionation, there was needed a greater interval between radiation exposures at 6°C than at 23°C to reduce lethal response. Cold exposure also enhances the response to reduced food intake after daily 75 R doses of X. Irradiated rats are able to survive longer in the cold on reduced food intake than non-irradiated.
In laboratory experiments with several animal species: rabbits (RB), rats (RT), hamsters (HM), guinea pigs (GP), and mice (MIC); these were exposed to X-Radiation at 25 R/min and 250 kvp whole body, to the total LD 50/30 for the given species, eg GP 200R, HM 500R, RT 600R, RD 800R, MC 675R. They were also exposed to Hypobaria (high altitude) and hypoxia, to 30,000-37,000 ft.; and Diet manipulation, including food deprivation. Treatments were: eg x-radiation, and ad lib food consumption with measurements of any anorexia for 3 days post irradiation, then 72 hrs later altitude exposure. Irradiated rabbits showed severe decrease in food consumption in the 3 day period, and increased hypoxia tolerance. GP and HM showed only slight decrease in hypoxic tolerance, with recovery in 24 hrs. MC, GP, HM showed no significant increase in hypoxic tolerance 3 days post radiation. Food lack increases altitude tolerance post rad all xc HM.

x-radiation, hypobaria, hypoxia, undernutrition, combined stresses, mortality, anorexia, altitude tolerance, interactive responses
**Alterations in Physiological Accommodation to Stress Induced by Irradiation**

In laboratory experiments, rats (young/adult/aged) were exposed to: NEUTRON RADIATION, to 220 Rad, fast neutrons from U Cal 60" cyclotron; and COLD, to -20°C. In one treatment, there was exposure to full dose of N, then C to -20°C during various times in a 30 day post radiation period. The neutrons impaired cold tolerance. At ½ dose neutrons caused loss of cold tolerance past 30 days, whereas x-radiation of similar dose caused tolerance loss with recovery of cold tolerance by day 22.

**KEY WORDS**

neutrons, cold, combined stresses, cyclotron, cold tolerance, interactive responses
In laboratory experiments, rats (195 F 6 wks old) were exposed to X-RADIATION (X) at 115 R/min, 500 R, 250 kvp, whole body; &/or BETA-RADIATION (B) from a Sr applicator, 38 R/sec, 500 R, to exposed adrenals; and COLD, 0°C 3h/day (C). Treatments involved exposures at different ages to various combinations of these. Life shortening occurred with 500R X whole body, but not with 500R B to adrenals. Cold exposure made no differences in these. But in total body irradiation, cold exposure can reduce slightly the acceleration of tumor onset associated with this radiation.
In laboratory experiments, rats (30) were exposed to: X-RADIATION (X) 25-27 R/min to 500 & 600 R, 250kvp filtered, whole body; and HYPOXIA in ascent and descent in chamber at 500 ft/min to 28,900 ft for 4 hrs, on days 1, 3, 5, 9, 15 of study. There was increased tolerance to lethal levels of hypoxia vs controls after X. This effect disappears 5 d after exposure to R both doses. If no food is taken for 72 hrs, the non-X animals increase tolerance to hypoxia just like the X animals. At 72 hr this increased time to asphyxiation is in part the consequence of post irradiation anorexia.
In laboratory experiments, dogs (28 Beagles, M, F, 4-13 yr) were exposed to X-RADIATION (X) 60-65 R/min, 270-1800 R, 1000 kvp; and HEAT, 105°F, RH 25%, breezy, up to 6 hr. Treatments included: X whole body 270 R; 97 R to upper body to xiphoid process; 1800 R localized to thyroid. It was found that whole body X damages the thermoregulation apparatus, so that a progressive increase in rectal temperature may occur, under various X + heat conditions. This depends on part of the body exposed to X. Upper body X does not produce much change in rectal temperature. Localized thyroid X lowers heat production, then rectal temperature. 
Radiosensitivity of Animals Exposed to Ionizing Radiation in an Altered Gaseous Medium

Vasin MV, Lvova TS, Antipov VV, Davidov BI, Koroleva LV, Petrukhin SV

USSR (site not given)

Radiobiol (USSR) 1980 (1);20:56-61

Limited information provided on laboratory experiments with mice (CBAxC57BL and C57BL) exposed to GAMMA RADIATION, from 60Co, 300-1000R, over 20 min; or HYPEROXIA, 100% Oxygen; and combinations of these. Inhalation of 100% Oxygen by intact animals elicits inhibition of mitotic activity in bone marrow, with no effects on cell fission in crypts of small intestine. But Oxygen enhances radiation injury of the small intestine, and protects bone marrow. This Oxygen effect is a function of radiation dose.

gamma radiation, oxygen, combined stresses, radioactive cobalt, hyperoxia, radiosensitivity, hemopoietic tissue, interactive responses

** continuation of title: "...2. A Comparative Study of Effect of Breathing Pure Normobaric Oxygen during Irradiation on the Radiosensitivity of Hemopoietic Tissue and Small Intestine (Rus)"
Effect of Sequential Exposure to Ionizing Radiation and to Heat on Antibody Production in Rats (Rus)

Gamzaeva IA, Gabai NS, Yagubov RF, Aivazova DK

Microbiol & Hyg Instit Baku USSR

Gig sanit (USSR) 1981 (1):35-36

In laboratory experiments, rats (40 Wistar) were exposed to: GAMMA RADIATION, from 60Co, total dose 0.11 Ci/kg, 7 hr/day; and HEAT, 40°C, 4 hr/day, for 7 mo. Treatments were: H, G, G then H. Long exposure to G reduced number of antibody-forming cells 18.3% in the spleen (after immunization with sheep RBC. H + G further reduced the number of antibody-forming cells.

gamma radiation, heat, combined stresses, antibody production, radiosensitivity, spleen, interactive responses
Effect on the Body of Increased Ambient Temperature Combined with Radiation (Rus)

Tsapkov MM

USSR (site not given)

Gig sanit (USSR) 1981 (1); 50-53

This brief paper compares experiments on mice, dogs, yeast cells, human lymphocytes, rats, humans, Chinese hamster ovarian cells, in exposure to: HEAT (H) 43-45° C; X-RADIATION 180 R/min, 700-1500 Rad separately and consecutively or simultaneously. There are discussed LD50 radiation sickness, development of myelitis, altered osteogenesis, respiratory rate, cell survival, enzyme activities, chromosome aberrations, hemopoiesis, etc. Synergistic and potentiation effects are considered.

heat, x-radiation, combined stresses, animal models, radiosensitivity, physiological responses, interactive responses
In laboratory experiments, rats (180 M Wistar) were exposed to: GAMMA RADIATION, from 60Co, 5.5 Gy, 0.005 Gy/sec; THERMAL BURN on 15% of body surface (source not discussed) applied within 10–20 min after G. G only and G + burn produce similar changes in histology of thymus, but the rate of recovery of cell count in thymus after combined exposure was lower than for G alone. Burn inhibits repair processes in thymus of irradiated animals.
In laboratory experiments, rats (147 F S-D) were exposed to: X-RADIATION, 7R/min 43 min exposures, total dose over 600 R; delivered in 8,7,7,7,7,7 min exposures with 7-8 min intervals between exposures, over period of 30 days; also VIBRATION (V), 0.5 in. dble ampl. (10 Gz peak), 20 Hz, 10 min exposure, given on day 7, 14, or 21 after irradiation. Radiation mortality at 30 days was 5-10%, V alone mortality was 34%. No differences were seen in V alone or V + X. There is very little in common in the action mechanisms: radiation having biochemical effects, and V having mechanical actions, and effects on vestibule and Cv reflexes.
In laboratory experiments, rats (170, in 7 groups), were exposed to: ACCELERATION, linear (G), 1.1-3.0 G, adjusted in 0.5G increments, continuously at constant level over 52 days (stopped a no. of times for feeding, observation), accompanied by rotation at 14 rpm; and GAMMA RADIATION (R) from Co at 91-94 Rads/min, with total to 700 Rads whole body. Treatment included: G (contin., selected level), then after "adaptation" to this, and 30-120 min after G off, 400 Rads, then return to 3 G or left at normal 1 G. Rats exposed to 2-3 G observed 4 mo showed no effects by day 7-14, and survive with suppressed body mass and reduced fat. X at 400 followed by 2 G showed increase in mortality, which was also higher at 3 G. Deceleration to normal G had then no influence on mortality. 3G + 700 Rads yielded 15/17 deaths. Thus continuous G after R increases radiation mortality.
Stress and Interstress Adaptation

Leblanc J

CANADA: Laval Univ Fac Med Dept Physiol Quebec.

Fed Proc 1969 (3); 28:996-1000

This surveys experiments done with rats (M) exposed to: HYPOBARIA, HYPOXIA, taken to 30,000 ft 1/hr, held there 4 min, and returned to ground level (total time 6 min), repeated 18x over 2 days; and COLD, -20°C for 3 hr. With H alone, evidence of adaptation by day 3. Repeated short exposures to C alone improve survival in the cold, providing a non-specific adaptation, improving tolerance to H when H + C are applied. There are speculations about endocrine mediation, especially norepinephrine.

hypobaria, hypoxia, cold, combined stresses, adaptations, endocrines, norepinephrine
In laboratory experiments, dogs were exposed to MICROWAVE RADIATION, 100 mW/cm², 2800 MHz, pulsed at 360 pps, with 2 usec pw whole body; and X-RADIATION, 4.6 R/min, 1656 R, 250 kvp. Treatment sequence was: x-rays; simultaneous microwaves and x-rays; 90 hr exposure to microwaves, then 9 mo later x-rays, whole body. Mortality was higher with x-rays and microwaves than with x-rays alone (hemopoietic death). Microwave treatment can increase lethal effect of x-radiation, as a function of MW duration, total dose, rectal temperature attained, time before x-rays, and x-ray dose.

**Key Words**
- microwave radiation
- x-radiation
- combined stresses
- mortality
- radiosensitivity
- hemopoiesis
- interactive responses
In laboratory experiments, rats were exposed to MICROWAVE RADIATION from 2450 Hz diathermy apparatus (no other data), and HEAT to head, at 40°C, 42°C, and 45°C, while in some experiments lowering core temperature to HYPOTHERMIA levels (values not given). In combined exposure to H and MR, survivals of 8-15 min seen with normothermic core temperature were increased up to 120 min in hypothermia. These prolongations existed even at brain temperatures to 45°C. It is believed that the integrity of the blood-brain barrier is violated when the brain is heated over 45 min at 40°C. Some testing of BBB integrity by detection of leakage at the cerebellum, was done with trace proteins, horseradish peroxidase.

**Key Words**

microwave radiation, hyperthermia, hypothermia, combined stresses, blood brain barrier, radiation protection, interactive responses
In laboratory experiments, mice (20 M adult) were exposed to BUTYLATED HYDROXYTOLUENE (BHT), dose 250 or 400 mg/kg IP lx; then after several days were exposed to OXYGEN, 100%, moist, for 24 hr. In measurement of incorporation of thymidine into pulmonary DNA: at 2, 3, 4 days after BHT, DNA synthesis was inhibited by 24 hr O2, 100%; at 5, 6, 7 days, there was no effect on synthesis. The same results were seen with incorporation of leucine into protein. The early proliferation of type I alveolar cells were more susceptible to cytotoxic effects of Oxygen than later interstitial and capillary endothelial cells.
Synergism of Hyperoxia and High Helium Pressures in the Causation of Convulsions

In laboratory experiments, mice (M adult CD) maintained at 33°C were exposed to HYPEROXIA (OHP) or high pO2, along with HIGH PRESSURE HELIUM (HP) in these treatments: compression in steps of 3 ATA at constant rate of 40, 100, 1000 atmo/hr; compression, but stops at a predetermined holding pressure; compression at 1000 atmo/hr but holding at one of several subconvulsive levels. The responses, high pressure neurological syndrome (HPNS) were Type I (involving hypothalamus, lateral thalamic nuclei, not cerebral cortex) and Type II (medial thalamus, cerebral cortex). HP + OHP beyond 1.8 ATA causes seizures at total HP lower than HP alone, for Type I but not Type II. This is not just an additive phenomena, but is CNS-selective. OHP exposure for 15 min is needed for OHP/HP lowering of I threshold. Type II may be influenced by indirect events, eg affecting cerebral blood flow.
In laboratory experiments, human subjects (12 M ages 23-40 yr, normal hearing) were exposed to SOUND (N) at 65 dbA or 100 dbA, 2.5-6.5 KHz flat, dropping at 5 db/octave below 2.5 KHz and 20 db/octave above 6.5 KHz, into headphones; VIBRATION (V) 0.36 Gz rms into hard seat, with spectrum a quasi-random sum of sines each at fatigue thresholds of 2.6, 4.1, 6.3, 10, 16 Hz. Treatments were: N(65); N(100); V + N(65); V + N(100); in random order in 4 sessions separated by 48 hr over 2 wk (after warmup, then 30 min exposure for a condition). Tasks were: complex counting (3 lights flash at 1 every 13 sec, 1/5 sec, 1/9 sec, all are counted with button for each light pressed every 6th flash). V + N100 causes less adverse effects than V + S65 (like earlier studies); V had a clear adverse effect on counting task; N100 also adverse effect on counting task.
Effects of Combined Heat, Noise, and Vibration Stress on Human Performance and Physiological Functions

Grether WF, Harris CS, Mohr GC, Nixon CW, Ohlbaum M, Sommer HC, Thaler VH, Veghte JH

AEROSP MED 1971 (Oct);42:1092-1097

In laboratory experiments, human subjects (10 M fit, in flight clothing) were exposed to SOUND (N) at 80 and 105 db, white noise flat from 100 Hz-5 KHz into earphones; VIBRATION (V) at 0.3 Gz peak, 5 Hz sine, into hard seat for 35 min; HEAT (H) 120°F. Treatments, after 1 hr pre-exposure to H when used:

H; V; N; V + N + H; after 30 min baseline data; 30-60 min: pre-exposure testing, at 60-65 min N and/or V; 65-95 min, exposures with performance testing, at 95-100 min, back to ambient; at 100-130 min post-exposure performance. Tasks: tracking (2-D compensatory), mental arithmetic, reaction time, visual acuity, voice communication. H alone affected heart rate, skin temperature, weight loss; H or V or N increased reaction time, decreased vigilance, impaired tracking, and visual acuity with V; combined stresses did no more than the single greatest stressor. No evidence of synergy.

sound, vibration, heat, combined stresses, psychomotor performance, physiological responses, interactive responses
In laboratory experiments, human subjects (6 M, 21-27 yr, unacclimatized) were exposed to HEAT (H), core temperature increases to 37.90°C, 38.20°C, 38.50°C were induced using a water suit, with core temperature raised and lowered in 2 consecutive events. Tasks included pursuit rotor test (pointer must be matched to position of lights on revolving arm) done for 60 sec at 3 points in each heating and cooling cycle; and work output on a bicycle ergometer. Performance was worse when core temperature was raised; decrements were 13.6% at 37.90°C, 16% at 38.20°C, and 18.1% at 38.50°C. There were differences in performance drops between heating and cooling phases, perhaps due to substantial differences in skin temperature.
In laboratory experiments, human subjects (12 M, fit) were exposed to SOUND (N) at 80 db and 105 db, broadband noise, into earphones for 35 min; VIBRATION (V) at 0.3Gz peak, 5 Hz sine, into hard seat, for 35 min; and HEAT (V) 120°F for 95 min. Treatments were: V; V + H; V + H + N; each session 95 min, with N or V applied 60 min after start; H applied at 0 time for 1 hour soak. Tasks were: 2-D compensatory tracking of dot in scope with RH controller; choice reaction time with lights to put on and off; telephone test with 24 voice messages and yes-no answers; mental arithmetic problems, visual acuity, and subjective rating of severity of stress. V alone induced the greatest errors in reaction time and tracking; errors were lower for V + H (marginally); and errors were lowest for V + H + N, an apparent antagonistic response.
In laboratory experiments, human subjects (12 M ages 19-23 yr, normal hearing) were exposed to SOUND (N) at 60 db or 100 db, 31.5 Hz-10 KHz (white noise) into earphones; VIBRATION (V) 0.10 G peak at 6.0 Hz into hard seat from shaker. Treatments were: N(60); N(100); V + N(60); V + N(100); randomized in 5 19-min trials, with 10 min rest, for total of 2.5 hr. Tasks: Tracking (centering of moving dot in circle in scope, with 2-axis RH control; and reaction time with lights on/off panel and LH switch. N alone had little consistent effect. V alone impaired 2 axis tracking. With V + N60 the effect was greater than V alone; V + N100 showed a smaller effect, thus a combined subtractive interaction. Speculations include arousal, inhibition of one sense by another.
In laboratory experiments, human subjects (12 M ages 19-24 yr, normal hearing) were exposed to SOUND (N) at 60 db or 110 db 31.5 Hz-16 KHz white noise into military earphones; VIBRATION (V) 0.10 Gz peak into hard seat from shaker. Treatments were: N(60); N(110); V + N(60); V + N (110), given in random 4 min exposure periods and 1 min rest totalling 79 min in a trial, with 11 min rest between trials and 3 trials/session in 4 sessions. Tasks: two axis tracking, centering moving dot into scope circle using 2-axis RH controller; and response time in switching pattern of lights (red lights off, green lights on with LH switch. N impaired tracking performance, V impaired tracking performance; N + V had an additive adverse effect. At this higher sound level N110 + V are additive, a switch from subtractive effect found in earlier study at N100 + V

sound, vibration, combined stresses, psychomotor performance, interactive responses
**Combined Effects of Noise and Vibration on Mental Performance as a Function of Time of Day**

In laboratory experiments, human subjects (10 M ages 23-30 yr, normal hearing) were exposed to SOUND (N) 85 db or 110 db, 31.5 Hz-16 KHz (white noise) into earphones; VIBRATION (V) 0.25 Gz peak at 5 Hz to hard seat from shaker. Treatments were: V+N(110) at 0600; N(85) at 0600; V+N(110) at 1500; N(85) at 1500. After 1 day practice, random exposures of 20 min 1/day for 4 days at 0600 or 1500. Tasks included arithmetic problems with displays presented and answers announced 18 x/session, scored for times to memorize and to calculate, and correct answers, for 6 problems. Performance was marginally deficient at 1500, compared with 0600 with N+V; without stresses, there was slight improvement at 1500 over 0600. Circadian cycle may intervene.

**KEY WORDS**

sound, vibration, combined stresses, psychomotor performance, time of day, circadian rhythms, arousal theory
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**DD FORM** 1 JAN 73 1473 (MOD.)
**Title:** Combination Effect of Ozone and Sulfur Dioxide on Pulmonary Function in Man

**Authors:** Hazucha M, Parent C, Bates DV

**In Laboratory Experiments,** human subjects (young, fit, non-smokers) were exposed to OZONE, 0.37 ppm or SULFUR DIOXIDE, 0.37 ppm or both simultaneously, for 2 hrs. Pulmonary function measurements were made every 30 min during and after exposure until all values had returned to pre-exposure levels. The combined stresses had much greater effects than each stressor alone. The most sensitive index was max expiratory flow rate (at 50% VC), which fell to 75% in 1 hr, then to 55% in 2 hr. Also dropping were lung capacity, closing and residual volumes. The same potentiating effects were seen with intermittent exercise. There was no discussion of mechanism of interaction.

**Keywords:** Ozone, sulfur dioxide, combined stresses, toxicity, pulmonary function, interactive responses
Clinical observations of a limited descriptive nature are provided concerning miners (50, ages 35-45 yr) in Stage 1 (USSR) of vibration disease; VIBRATION exposure derived from mining tools, over 15 yr period. This group was treated in two ways: with CONSTANT MAGNETIC FIELD (CMF) of 150-200 oersted, in 20 exposures, each of 15-20 min; and with THERAPEUTIC DRUGS, such as sympatholytics, spasmolytics, ganglionic blockade agents. The CMF responses were stated as analgesic, "normalizing" blood pressure and vascular tonus, and effective in inhibition of catecholamine in excretions.

vibration, magnetic fields, combined stresses, mining, vibration syndrome, biomagnetism
CHEMICAL/PHYSICAL
COMBINED STRESS EXTRACTS
Review of Environmental Factors Affecting Hearing

Mills JH, Going JA

Med Univ SC Dept Otolar Charleston

Environ Hlth Perspect 1982 (4);44:119-127

Topics include: impulse noise (impact, intermittent) and steady noises, differences and synergies in effects on cochlea, the role of reflex response; noise and aminoglycoside antibiotics, as examples of synergistic actions on cochlea; industrial study problems, noise measurement, contamination by other environmental factors, standards, disability, work performance; aging and presbycusis, sites of pathology; viral damage to hearing, cytomegaloviruses, rubella, etc.; and a long array of toxic chemical factors.

sound, noise, hearing, combined stresses, antibiotics, toxic chemicals impulse noise, cochlear damage, presbycusis, other interactive responses, hearing disability
In laboratory experiments, rats (M adult SD) were exposed to:
CHLORPROMAZINE (CPZ) IV 100 ug or L-TRYPTOPHAN IV 200 mg/Kg under restraint; to induce hypothermia they were housed in COLD at 4°C. When appropriate Tcore of 32-33°C was reached (in 40-60 min), rats were exposed to HEAT, at 35°C, and EXERCISE on treadmill until hyperthermic exhaustion. Initial temperature has a major effect of endurance capacity; initial hypothermia prolongs time to hyperthermic exhaustion. These CPZ or TRY improved running times had no extra beneficial effect on thermoregulatory cooling rates after exhaustion.

**KEY WORDS**
chlorpromazine, l-tryptophan, combined stress, exercise, hyperthermia, exhaustion, hypothermia, interactive responses
Chronic Chlorpromazine Administration in Rats: Effects on the Ability to Work in the Heat

In laboratory experiments, rats (M CD) were exposed to: CHLORPROMAZINE at 2 mg IP for 250-350 g rats for 14 consec days; then were exposed to HEAT at 35°C and EXERCISE on treadmill to hyperthermic exhaustion (Tcore to 42.5-43°C). Chlorpromazine increased plasma lactate, reduced endurance, increased body heating and raised Tcore on treadmill, all toward injury endpoints. Thus CPZ reduces ability to work in the heat.

chlorpromazine, heat, combined stresses, exercise, work, heat exhaustion, thermoregulation, hyperthermia, interactive responses
# Interactions, Range Effects, and Comparisons Between Tasks in Experiments Measuring Performance with Pairs of Stresses: Mild Heat and 1 Mg of L-Hyoscine Hydrobromide

## Authors
Poulton EC, Edwards RS

## Publications
Aerosp Med 1974 (July); 45:735-741

## Extract
In laboratory experiments, human subjects (12 M 18-27 yr) were exposed to HEAT, 38°C; also L-HYOSCINE hydrobromide at 1 mg, given 1.5 hr earlier. Performance measurements included: tracking (compensatory) with system of lights, multichoice light and stylus-touch system, Wilkinson auditory vigilance task (with irregular auditory cues). The order of testing was important in determining combined stress-response interactions. L-hyoscine alone or heat alone increased response time. L-H + heat were synergistic, with greater reduction in response times than the separate stressors produced. Vigilance response was most affected.

## Keywords
hyoscine, heat, combined response, psychomotor performance, vigilance, tracking, interactive responses
In laboratory experiments, dogs (M) were exposed to: HYPOBARIA with normoxia, to simulated 27,000 ft but with 100% oxygen supply at gnd level by mask; also CHLORPROMAZINE at 2.5 mg/Kg IV. Altitude exposure was for 30 min. Glucose tolerance after 20% glucose IV was measured. The most rapid rate of glucose elimination occurred at ground level with chlorpromazine. This rate is cut by 50% with chlorpromazine is given with altitude exposure. The CPZ also exerts its basic effects in lowering systemic blood pressure and core temperature.
Effects of Reduced Pressure and Drug Administration on Glucose Tolerance Test in the Dog

In laboratory experiments, dogs (M) were exposed to: HYPOBARIA without hypoxia, to 27,000 ft but given 100% sea level Oxygen by mask; and given AMPHETAMINE at 1 mg/Kg IV, or BENADRYL 2 mg/Kg IV, or DEMEROL at 1.8 mg/Kg IV. Glucose tolerance was measured. There was increased glucose elimination with hypobaria. Each drug alone also enhanced glucose elimination. Except for Demerol, benadryl or amphetamine + altitude increased glucose decay. Also the basic effects of amphetamine as analeptic, increasing blood pressure and respiration; and of Benadryl as antihistaminic and vasodilator; and of demerol as hypotensive agent were seen.

**Key Words**
- hypobaria
- therapeutic drugs
- combined responses
- amphetamine
- benadryl
- demerol
- glucose tolerance
- interactive responses

**Notes**
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4. TITLE (and Subtitle)
Cardiorespiratory Assessment of Decongestant-Antihistamine Effects on Altitude, +Gz, and Fatigue Tolerances

5. TYPE OF REPORT & PERIOD COVERED
Jnl article

6. PERFORMING ORG. REPORT NUMBER
FAA-OAM-78-20

7. AUTHOR(s)
Lategola MT, Davis AW Jr, Lyne PJ, Burr MJ

8. CONTRACT OR GRANT NUMBER(s)

9. PERFORMING ORGANIZATION NAME AND ADDRESS
FAA Civil Aeromed Institut Okla City

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS

11. CONTROLLING OFFICE NAME AND ADDRESS

12. REPORT DATE
1979

13. NUMBER OF PAGES AND REFS
9P 16R

14. PUBLICATION
Aviat Space Environ Med 1979 (Feb); 50:101-109

15. SECURITY CLASS. (of this report)

16. DISTRIBUTION

17. ABSTRACT
In laboratory experiments, human subjects (M adult) were exposed to: HYPOBARIA, HYPOXIA at 12,500 ft simulated altitude, for 2 hr; DRISTAN (phenylephrine + phenindamine + aspirin + caffeine etc); or ACTIFED (pseudoephrine + tripolidine); and ACCELERATION SIMULATION (Gz) using lower body clothing which applied a -40 mm Hg pressure to extremities, for 2 hrs. These stresses were applied in various combined treatments. All combinations of one of the two drugs, altitude, Gz were tolerated well (except for an actifed-altitude interaction on heart rate, enhanced when the simulated Gz is applied). Also, neither drug has effect on short duration post altitude ergometer fatigue.

18. KEY WORDS
antihistaminics, decongestants, hypobaria, combined stresses, altitude, fatigue, exercise, dristan, actifed, interactive responses

19. NOTES

20. DD FORM 1473 (MOD.)
In laboratory experiments, human subjects (14 M 18-33 yr) were exposed to: HYPOBARIA, HYPOXIA at 12,500 ft simulated for 2 hr, after prior dose of: DRISTAN (phenylephrine + phenindamine + aspirin + caffeine + etc) or ACTIFED (pseudoephedrine + tripolidine). Observations were made of fatigue, performance on multiple task batteries, heart rate, blood pressure, temp etc. While fatigue went up with time, task performance showed no effects of altitude, drugs, or time. One response, heart rate showed increases significantly higher at altitude with the Actifed (which acted as a stimulant) in magnitude more than the sum of effects of Actifed or altitude.
**Title**: The Effect of Hyperbaric Helium-Oxygen on the Acute Toxicity of Several Drugs

**Authors**: Small A

**Performing Organization**: USN Med Res Inst Bethesda MD

**Publication**: Toxicol Appl Pharmacol 1970;17:250-261

**Extract**: In laboratory experiments, rats (M, SD) and mice were exposed to: HYPERBARIA, with Helium 19.2 atmo--Oxygen 0.2 atmo mix for 45 min then were given these drugs: PENTOBARBITAL 40 mg/kg iv (lethal dose), to rats; LIDOCAINE to rats 9.75 mg/ml given iv at 0.2 ml/min (lethal dose); ETHANOL to rats 0.104 ml/min iv (lethal dose); MORPHINE to rats IV at LD50 level; and ASPIRIN to mice po at LD50 level. Drugs were given separately. The 2-hr LD was determined by slow infusion to point of cardiac arrest (xc aspirin oral 3 hr mortality). The acute toxicity of all drugs used was not altered by exposure to the hyperbaric environment. This does not speak for any altered therapeutic effectiveness in these same environments.

**Key Words**: hyperbaria, therapeutic drugs, combined stresses, heliox mixtures, cardiac arrest, acute toxicity, lidocaine, pentobarbital, ethanol, morphine, aspirin, interactive responses

**Notes**: 

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**DD FORM**: 1473 (MOD.)
In laboratory experiments, mice (CD) were exposed to HYPERBARIA with Helium at 2 atm/min to 125 ATA, 30 min after administration of these anesthetics to different groups: PHENOBARBITAL .17 g/Kg IP, alpha-chloralose to 0.04 g/Kg IP, ethyl carbamate to 1.45 g/Kg IP, Argon to 24.2 atmo, and Nitrogen to 48.8 atmo. Righting reflexes and sleep duration were observed. The potencies of anesthetics can be reversed in hyperbaria, eg ED$_{50}$ 1 atmo:1 atmo for a-chloralose is 1.74, for ethyl carbamate 1.64, for phenobarbital 1.54, for Argon 1.36, and for Nitrogen 1.34. These increased ED$_{50}$ were linear functions of pressure. The author discusses in this context alternate fluidized membrane or critical volume hypotheses of anesthesia.

**Key Words:**
anesthesia, hyperbaria, combined stresses, phenobarbital, alpha-chloralose, ethyl carbamate, argon, nitrogen, helium, sleep, interactive responses
In laboratory experiments, mice were exposed to: HYPERBARIA, with Helium to 100 ATA; and ANESTHESIA induced by Nitrogen or Argon. Ar or N₂ abolished righting reflexes in 50% at Helium high pressure. At 100 ATA to attain anesthesia requires 55% more Argon or 27% more Nitrogen. This antagonism by Helium is not a simple reciprocal relation.
Workplace observations and clinical studies were made on workers exposed to SOUND and to MERCURY VAPORS (at approximate levels used in experiments below); 190 men were observed at some times over a 5-10 yr work exposure period. Sound alone produced signs of cochlear neuritis (from cochlear potential changes) and hearing disorders. Sound enhanced mercury induced hearing loss (measured audiometrically). In lab experiments, guinea pigs (18) were exposed to SOUND (S) at 94-105 dbA (no other data) and MERCURY VAPOR (M) 0.023-0.037 mg/m³. S + M produced 2-3 X the biopotential change of M alone, showing also cochlear and auditory nerve mixed types of damage, toxic labyrinthitis and neuritis. There is limited discussion of the different dystrophic mechanisms and interactions on these sensory targets.
**Extract**

In laboratory experiments, rats (F, random bred) were exposed to: VIBRATION (V), 0.44 mm displacement, 48-52 Hz sine, whole body, direction not given, 3 hr/day for 12 wk; and ETHYL MercURY ChlorIDE (EMC) (tagged with ²⁰³Hg, 0.58 uCi) once every 2 days, for 3, 7, or 12 wk, with total dose of 4, 9, or 12 mg. Treatments were: V + EMC, V+EMC then V alone for 4 wks, or V for 3, 12 wk then EMC 1 time at 1 mg. EMC + V for 3 and 12 wk resulted in changes in Hg metabolism, even after stopping the EMC; there was delayed excretion, increased accumulation, which cleared up in part in 12 wks, even during concurrent administration. V + EMC (1 time, 1 mg) had same effect. The combination somehow causes changes in Hg distribution, and may alter vascular permeability of blood brain barrier.

**Key words**

vibration, ethylmercurychloride, combined stresses, organomercury, chemical toxics, metabolism, vascular permeability, toxics clearance, interactive responses
Combined Effects of Physical and Chemical Factors during Industrial Applications of Plasma Processes (Rus)

Ilinskaya AV, Koroleva VA, Levin AI

Instit Hyg, Moscow, USSR

Gig san (USSR) 1981 (1); 30-32

Workplace observations in welding and cutting activities, on 97 employees (ages 24-43 yr, exposed for 3-12 yr) concerned exposures to SOUND (S) 120-130dBa at 4, 6, 8 KHz; or ULTRAVIOLET RADIATION, 7.4 W/m² 26-340 nM; of mixes of OZONE and NITROGEN OXIDES in aerosols (values not avail). Changes were reported in this combined stressor exposure, chiefly autonomic and neurasthenic syndromes, also progressive hearing losses, altered EEG alpha, and certain responses to photic stimulation, vascular disturbances including cerebral blood flow, and EKG changes. No other data are available.

sound, ultraviolet radiation, ozone, nitrogen oxides, combined stresses, welding industry, autonomic disturbances, EEG, EKG, cerebral blood flow, neurasthenia, neuropathology, interactive responses
In laboratory experiments, rats (albino) were exposed to:

- **BENZENE**: 5, 15 mg/m³ by inhalation for 5 mo, or 0.5 g/kg sc 2x/wk for 3 wk (B);
- **VIBRATION**: 80 db at 16 Hz (no other data) (V);
- **SOUND** from 66 db to MPL (no other data) (S).

Treatments were: Binhal + V + S, Binhal + V; or Bsc + V, Bsc + S.

Observations were made of body wt, respiratory rate, heart rate, rbc count, hemoglobin level, blood chemistry, and various reflexes. V and S potentiated the effects of Binhal or Bsc. V + B + S yielded enhanced effects, threshold shifts, and morphological changes even when B was kept at MPC threshold. It is recommended in combined exposures, the MPC be decreased from single exposure levels for each stressor here.

**Key Words**
- benzene, vibration, sound, combined stresses, toxicity, chronic exposures, MPC and MPL modifications, interactive responses
**Title:** Investigation of Combined Action of Vibration and Lead on Metabolism of the Liver and Kidneys in Albino Rats (Rus)

**Authors:** Antov GP, Ivanovich E, Zapryanov Z

**Publication:** Gig trud (USSR) 1978 (5); 54-56

**Extract:**

In laboratory experiments, rats (M Wistar age 3 mo) were exposed to: VIBRATION (V) 0.01 mm amplitude at 100 Hz 2 hr/day for 10 days (no other data avail), and/or LEAD ACETATE, 20 mg/Kg po 1/day for 10 days. Extensive measurements of liver and kidney metabolism included succinate dehydrogenase, malate dehydrogenase, LDH, G-6-PDH, cytochrome oxidase, alkaline phosphatase, acid phosphatase, isocitrate dehydrogenase, ATPase, glucose-6-phosphatase, etc. V and Pb have an additive effect on most of these; V affects distribution and accumulation of Pb and enhances its toxicity.

**Keywords:** vibration, lead acetate, combined stresses, liver enzymes, kidney enzymes, metabolism, interactive responses
An Analysis of the Degree of Influence of Environmental Factors with Multiple Combined Effects (Rus)

Sova RE, Tsapko VG, Gokhman VL

Instit Hyg, Kiev, USSR

Gig trud (USSR) 1974 (2); 46-48

In laboratory experiments, lab animals (no other data) were exposed to: SOUND (no other data); CHLOROPHOSPHATE INSECTICIDES at 1/20 LD$_{50}$ (no other data), in various combinations, and measurements such as cholinesterase activity were made. The report provides analytical statistical model for multiple combined effects, with limited information.
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<tr>
<td>The Problem of Combined Action of Phosphorus Organic Pesticides and Noise on the Body of Warm Blooded Organisms (Rus)</td>
<td>Jnl article</td>
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<th>7. AUTHOR(s)</th>
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<td>Tsapko VG</td>
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<td>Sci Res Instit Hyg, Kiev, USSR</td>
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<td></td>
<td>1976</td>
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<td>Gig sanit (USSR) 1976 (5);32-35</td>
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<tr>
<th>16. EXTRACT</th>
<th>17. KEY WORDS</th>
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<tbody>
<tr>
<td>In laboratory experiments, lab animals (not specified) were exposed to: DIPTEREX (chlorophose) at 0.5 mg/m³ (MPL) or 2 mg/m³; and SOUND at 85 or 105 dBA (no other data) in exposures to both at 2 hr/day for 4 mo. Measurements included: cholinesterase activity, indices of natural immunity (complement, lysozyme, B-lysine, blood bacticidal activity, phagocytic activity of neutrophils). D (0.5) + S (85) caused inhibition of cholinesterase activity. D (0.5) + S (105) caused further reduction. D (2.0) + S (85 or 105) further inhibited cholinesterase, in combined potentiating effects, including changes in immunologic factors. It is recommended that permissible levels for single stressors be reduced when they comprise combined exposures.</td>
<td>sound, dipterex insecticide, combined stresses, cholinesterase, natural immunity, immunopathology, organophosphates, toxicity, interactive responses</td>
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<th>18. DISTRIBUTION</th>
<th>19. NOTES</th>
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**Effect of Motor Transport Noise and Atmospheric Air Gases on the Organism (Rus)**

In experiments simulating urban exposures to traffic conditions, laboratory animals (unspecified) were exposed to SOUND in range of traffic noise to 80 dbA (no other data), and CARBON MONOXIDE at 0.66-20.0 mg/m³. Measurements were made during combined exposures for 3 mo, of body wt, bioelectric activity of cerebral cortex, cholinesterase activity, etc. The combined exposures produced certain inhibitions of CNS activity. Each factor alone caused no action at the doses stated. No other data are provided.

**KEY WORDS**

- sound
- carbon monoxide
- combined stresses
- urban traffic
- cholinesterase
- air pollution
- toxicity
- neuropathology
- interactive responses
<table>
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<th>5. TYPE OF REPORT &amp; PERIOD COVERED</th>
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<tr>
<td>The Joint Action of Environmental Factors in Industry and Their Standardization (Rus)</td>
<td>Jnl article</td>
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<tr>
<th>7. AUTHOR(s)</th>
<th>8. CONTRACT OR GRANT NUMBER(s)</th>
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<tr>
<td>Tarasenko NY, Kasparov AA, Smirnova EM, Ananiev BV</td>
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<td>First Moscow Med Instit, USSR</td>
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<td></td>
<td>1971</td>
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<tr>
<td>6P 18R</td>
<td>Gig san (USSR) 1971 (7);27-32</td>
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<th>15. EXTRACT</th>
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<td>Occupational observations were made of chemical industry workers in boric acid production, who were exposed to: SOUND (no other data), HEAT (no other data), BORIC ACID and various TOXIC CHEMICALS (not specified); in various patterns of combined exposure on the job. The joint stresses enhance the losses of hearing (audiometric), beyond exposure to sound alone. It recommended that in the establishment of industrial microclimate standards, that permissible levels (at least of sound) be lowered when combined stresses are encountered.</td>
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<tr>
<th>16. KEY WORDS</th>
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<tr>
<td>heat, sound, boric acid, combined stresses, toxic chemicals chemical industry, toxic chemicals, hearing loss, permissible level standards, interactive responses</td>
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| 20. NOTES |
Radiosensitivity of Animals Exposed to Ionizing Radiation in a Modified Gaseous Medium

In several laboratory experiments, rats, mice, dogs (no other data provided) were exposed to: RADIOPROTECTIVE AGENTS, Cystamine at 100 mg/Kg, or Mexamine at 25 mg/Kg, given 3-5 min before GAMMA RADIATION from 60Co, 700-1100 R, with subjects in OXYGEN 100% atmosphere (sea level). Observations were made of 30-day survival, life span, hematology. Oxygen decreased the radioprotective effect of cystamine or mexamine (5-methoxytryptamine) in animals (not specified), with faster development of leucopenia and more pronounced intestinal syndrome.

Key Words: radioprotective agents, gamma radiation, combined stresses, cystamine, mexamine, 5-methoxytryptamine, radiation sensitivity, leucopenia, intestinal syndrome, radiation sickness, interactive responses

Notes: *** Title contd.: "...1. Effect of Breathing Pure Normobaric Oxygen During Irradiation on Radioresistance and Effectiveness of Radioprotective Agents" (Rus)
In laboratory experiments, guinea pigs were exposed to: KETAMINE at 1-25 mg/Kg or THIOPENTAL at 2-3 mg/Kg each iv, then these treatments: Air at 1 ATA, He-O₂ at 1 ATA, Heliox at 20 ATA, Heliox at 31 ATA. Hyperbaria increased the induction doses required and decreased the duration of sleep. There was less pressure antagonism with ketamine than thiopental.
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<th>REPORT DOCUMENTATION PAGE</th>
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<tr>
<td>1 REPORT NUMBER</td>
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<tr>
<td>4 TITLE (and Subtitle)</td>
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<tr>
<td>Dose-Responses of Guinea Pigs to Diazepam at Recompression Depths</td>
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<td>7 AUTHOR(S)</td>
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<tr>
<td>Nicodemus HF, Bailey RC, Summe JP, McElroy H</td>
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<td>10. PERFORMING ORGANIZATION NAME AND ADDRESS</td>
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<td>13. PUBLICATION</td>
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<tr>
<td>Undersea Biomed Res 1980 (Mar);7:1-7</td>
</tr>
<tr>
<td>16 EXTRACT</td>
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<tr>
<td>In laboratory experiments, guinea pigs (M) were exposed to: DIAZEPAM at 0.02-2.0mg/Kg iv, after exposure to HYPERBARIA, with compression at 0.1 ATA/sec to either 3ATA of oxygen or 3-6 ATA of air. Duration of sleep was observed. There is a shorter duration of sleep in the hyperbaric groups. Less drug was needed to induce sleep in hyperbaric air at 3 ATA and more was needed in hyperbaric oxygen. Synergism may not be evident when thresholds for stimulating effects of pressure are exceeded.</td>
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<td>18. KEY WORDS</td>
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<td>hyperbaria, diazepam, combined stresses, sleep, compression, hyperoxia, interactive responses</td>
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DD FORM 1 JAN 73 1473 (MOD.)
Acute Toxicity of Histamine and Tripelennamine in Animals Exposed to Hyperbaric Helium

Small A, McElroy HW, Ide RS

USN Med Res Inst Bethesda MD

1973;26:418-425

In laboratory experiments rats (SD) and guinea pigs (Hartley) were exposed to HYPERBARIA, equilibrated to He 19 ATA + O₂ 0.2 ATA. Rats also received TRIPLENNAMINE IV to doses of about 8.6 mg/Kg, and guinea pigs received HISTAMINE toward lethal dose of 300 µg/Kg, but halted at onset of cardiac arrhythmias induced by asphyxia. There was no effect of hyperbaric He 19 ATA + O₂ 0.2 ATA on the toxicity of tripelennamine in rats, nor on the toxicity of histamine in guinea pigs; but TPA toxicity studies in guinea pigs suggests that hyperbaric He has a potentiating effect on response.

hyperbaria, tripelennamine, combined stresses, asphyxia, arrhythmia, interactive responses
**Extract**

This review discusses exposure conditions from 0.3 ATA-200 ATA. The comparative biological effects of hyperbaria alone are considered, along with the biological effects of inert gases. The combined factors of altered pressures and inert gases on toxicity of such exogenous agents as carbon monoxide, ozone, nitrogen dioxide, carbon tetrachloride are discussed. Problems encountered in these atmospheres with therapeutic agents such as morphine, digoxin, anesthetics (including anesthetic reversals) and the pharmacological therapy of decompression sickness are all reviewed.

**Key Words**

hyperbaria, toxic substances, combined stresses, anesthesia, therapeutic drugs, decompression sickness, oxygen toxicity, interactive responses
**Combined Effects of Noise and Ototoxic Drugs**

This review includes these topics: legislation concerning noise; noise-induced "ototoxicity" considering trauma vs continuous exposure, permanent damage conditions, dependence on sound spectrum, modes of destruction and pathology; drug-induced ototoxicity, for salicylates and quinine, for diuretics (eg ethycrynic acid, furosemide) and related cochlear damages with swollen endothelial cells, mitochondrial pathology, also for aminoglycoside antibiotics (streptomycin, kanamycin, neomycin, gentamycin), with discussions of changes in endolymph electrolytes, aggravated problems in renal failure. Also discussed is combined stress ototoxicity, and of possible synergies and sensitization by noise of hair cells to antibiotics damage. Speculations are included about cochlear vasoconstriction, endocochlear potential changes, membrane permeance alteration, and Na/K ATPase inhibition.

**Key Words**

- sound, ototoxic drugs, combined stresses, hearing, cochlear damage, ototoxic drugs, salicylates, diuretics, aminoglycoside antibiotics, interactive responses
In laboratory experiments, guinea pigs (20+) were exposed to: SOUND (S), 115 db, filtered noise of 1 octave centered at 8 KHz for 70 hr; and NEOMYCIN (A) at 200 mg/Kg im 1/day for 7 days. The 8 KHz frequency was selected to produce damage, if any, to basal turn of cochlea, where hair cell damage has been max after neomycin. Treatments were: S, A, S + A. Studies were made of cochlea 2 wks after treatment. Each agent caused loss in cochlear potential, mapped as cochleogram; combined losses are greater than the 2 losses summed. Histological damage also is much greater than simply additive. Neomycin may sensitize the hair cells and enhance their response to mechanical trauma.

**KEY WORDS**

sound, neomycin, aminoglycoside antibiotic, combined stresses, chemical toxics, hair cells, cochlea, hearing loss, pathology, interactive response
<table>
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<tr>
<th>1. TITLE (and Subtitle)</th>
<th>Aminoxyacetic Acid Protects Against Noise-Induced Cochlear Hair Cell Loss</th>
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<tr>
<td>2. TYPE OF REPORT &amp; PERIOD COVERED</td>
<td>abstract</td>
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<td>3. AUTHOR(s)</td>
<td>Bobbin RP, Guth MS, Mines AB</td>
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| 4. CONTRACT OR GRANT NUMBER(s) | G: NIH NS 11647  
G: NIH NS 10463 |
| 5. PERFORMING ORG. REPORT NUMBER | |
| 6. PERFORMING ORGANIZATION NAME AND ADDRESS | La State Univ Med Ctr Dept Otolar, Kresge Hrg Res Lab, New Orleans |
| 7. CONTROLLING OFFICE NAME AND ADDRESS | |
| 8. REPORT DATE | 1975 |
| 9. NUMBER OF PAGES AND REFs | 1P no R |
| 10. PUBLICATION | J Acoust Soc Am  
1975 (Suppl 1); 58:589 (abstract) |
| 11. KEY WORDS | sound, aminooxyacetic acid, combined stresses, hearing loss, cochlear damage, hair cells, toxicity, chemical protectants, interactive responses |
| 12. REPORT NUMBER | |
| 13. CONTRACT OR GRANT NUMBER | |
| 14. NUMBER OF PAGES AND REFs | 1P no R |
| 15. SECURITY CLASS. | |
| 16. EXTRACT | In laboratory experiments, guinea pigs were pretreated with: AMINOOXYACETIC ACID (AOAA) at 20 mg/Kg sc, then exposed to SOUND (S) at 126 db, 4 KHZ sine, for 30 min. They were sacrificed at 21 days and hair cells counted. There was a lower loss of hair cells with AOAA + S than with S alone. There are speculations about the relationship of endocochlear potentials and noise-induced hair cell destruction. No other information is available. |
| 17. KEY WORDS | sound, aminooxyacetic acid, combined stresses, hearing loss, cochlear damage, hair cells, toxicity, chemical protectants, interactive responses |
| 18. NOTES | |
| 19. DISTRIBUTION | |

**In laboratory experiments, guinea pigs were pretreated with:**

**AMINOOXYACETIC ACID (AOAA)** at 20 mg/Kg sc, then exposed to **SOUND (S)** at 126 db, 4 KHZ sine, for 30 min. They were sacrificed at 21 days and hair cells counted. There was a lower loss of hair cells with AOAA + S than with S alone. There are speculations about the relationship of endocochlear potentials and noise-induced hair cell destruction. No other information is available.
In laboratory experiments, guinea pigs were exposed to: SOUND (S) 68-72 db, 125 Hz (as found in their baby incubators); and KANAMYCIN (A) at 15-100 mg/Kg, 1/day for 3, 5 wk. A alone at 15, 50, or 100 mg/kg for 3 or 5 wk showed here no significant hair cell loss on any repeated turns. S alone for 5 wk caused only small hair cell damage. S + A (15,50 mg/Kg) for 3 wk caused no hair cell loss; but S + A (50) for 5 wk yielded the worst damage to outer hair cells. A(100) for 5 wk caused no substantial loss; S + A (100) for 3 wk caused early and extensive hair cell damage.
<table>
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<th>Noise and Kanamycin Interaction in Guinea Pig Cochlea</th>
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<tr>
<td>Author(s)</td>
<td>Hawkins JE Jr, Marques DM, Clark CS</td>
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<tr>
<td>Performing Organization Name and Address</td>
<td>Univ Mich Schl Med, Hrg Res Inst Ann Arbor</td>
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<tr>
<td>Publication</td>
<td>J Acoust Soc Am 1975 (Suppl 1); 58:589 (abstract)</td>
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In laboratory experiments, guinea pigs were exposed to:
SOUND (S), at 90, 100, 106 dbA; in octave bands at 0.1, 2, 8 KHz or with broadband noise, for 8 hr/day and 7 days; also
KANAMYCIN, at 100 mg/Kg sc 1/day (A). Treatments were: S, A, or S + A. Cochlear injuries studied included reduction in cochlear microphonics or neural potentials, and loss of hair cells.
S + A showed interactive effects (potentiation) at S levels over 100 db in some animals for most frequencies; but at 0.5 KHz, even at 112 db, which damages turn 3 in cochlea, there was no enhancement of damage by the A at this region.

Key Words
sound, kanamycin, combined stresses, hearing loss, hair cells, cochlea, microphonics, aminoglycoside antibiotics, interactive responses
In laboratory experiments, guinea pigs (50, 25-450 gm) were exposed to: SOUND, 115 dbA white noise 10 hr/day for 7 days (S); and KANAMYCIN antibiotic (A) at 200, 300, 400 mg/Kg sc 1/day for 7 days, given before exposure to sound. Treatments were: S, A (200, 300, 400), and S + A (200, 300, 400) given in 7 days exposure, then 30-40 days to stabilize any damage. Cochlear damage was determined by electrophysiological and morphological technics. S + A (300 mg/kg) show cochlear damage 4 x the sum of either stress alone (synergy), to outer hair cells, which are destroyed by S or A alone. A at 400 mg/Kg alone causes severe effects, more than 2 x 200 mg/Kg doses, and could mask S effects in combined exposure. S itself does not change pharmacokinetic effects, but may change local vascular sufficiency, producing hair cell ischemia and hypoxia.

19. KEY WORDS
sound, neomycin, combined stresses, aminoglycoside antibiotics, toxicity, cochlear damage, hair cells, hearing loss, interactive responses.
In laboratory experiments, guinea pigs (M, 35+) were exposed to: SOUND, 90 db OAL, white noise (down to 63 db at 35.5 Hz+ octave, and 52 db at 31,500 Hz+ octave), from loudspeaker, for 5 wk (S); and KANAMYCIN, at 100 mr/Kg (route not avail) 1/day for 5 wk (A). Treatments were: S, A, S + A. Combined exposure with S + A has a potentiating damage effect, with max damage over 1 KHz. Hair cell losses occur in two places in the cochlea: at the apex, in the third row of outer hair cells (OHC), and in rows 1 and 2 of OHC.
Combined Effects of Noise and Neomycin: Cochlear Changes in the Guinea Pig

Brown JJ, Brummett RE, Meikle MB, Vernon J

Univ Oreg Hlth Sci Ctr, Kresge Hrg Res Lab, Portland

Acta Otolaryngol (Stockh) 1978; 80: 394-400

In laboratory experiments, guinea pigs (32) were exposed to:
SOUND, 115 dbA broad band white noise, 10 hr/day for 7 days (S); and
NEOMYCIN antibiotic (A) at 200 mg/Kg sc 1/day for 7 days,
given before exposure to sound. Treatments were: A + S, S, A,
in 7 days exposure, then 30-40 days to stabilize any damage. Cochlear potential was recorded using sound stimulation at 16 frequencies 100 Hz-20 KHz, and histopathology to show any missing hair cells. S alone caused 16 db loss, A alone caused 7 db loss, and may interfere with lipids relating to otolith permeability. S or A damage different parts of the cochlea. S + A have a marked interaction, causing 62 db loss, and nearly 100% hair cell loss (the S hair cell loss is 18%, the A hair cell loss is 25%).

KEY WORDS
sound, neomycin, combined stresses, aminoglycoside antibiotics, toxicity, cochlear potentials, hair cells, hearing loss, interactive responses.
In laboratory experiments, mice (LAFl/J) were exposed to: ULTRASOUND (diagnostic equipment, no other data) applied to mothers and fetuses not at term; also PROTEIN-DEFICIENT DIET with content well below the 20% casein/15% fat components optimum for fetal growth. Ultrasonic exposure under deficient diet conditions (marginally) decreased fetal and placental weight gains, and cell DNA/RNA content.
In laboratory experiments, mice (one group normal, resistant to audiogenic seizure, second group GFF genetically deaf subline, verified by cochlear microphonics and evoked potential) were exposed to: SOUND, either 60 db at 10 KHz or 100-106 db at 6-50 Hz (infrasound) from speakers, for 2 hrs before swimming; also ETHANOL, 275-340 mg/Kg in 10% soln, given 0.5-3.0 hr before swimming (this dose produces very low blood levels, 15-25 mg%); EXERCISE, swimming time survival, with weight tied onto tail. Eth alone had no significant effects on swimming, nor did infrasound. Alcohol interactions (occurring only when ingested within 90 min before or at same time as 2nd event): Eth + infrasound have additive effects on reduced swim time; infrasound aggravates Eth effect, prolongs Eth impairment in deaf mice (so non-auditory autonomic change) and normals; no interaction between Eth + 10 KHz S.
In laboratory experiments, rats (170 M albino) were exposed to:

- VIBRATION (V): 0.1 mm amplitude, 40-100 Hz, whole body, direction uncertain, 2 hr/day x 10 day; SOUND (N): 105 dbA, white noise, 2 hr/day x 10 day; HEAT (H): 35°C (45-55% RH, 0.2-0.3 M/sec air) 2 hr/day x 10 day; and LEAD ACETATE (Pb): 20 mg/Kg oral, 1/d x 10d.

Treatments included V+N, V+H, V+C. Liver changes: morphology, enzymes (e.g., succinic dehydrogenase, LDH, ATPase), soluble proteins and chemistry (in slices) were measured. V causes no marked change in chemistry and enzymes, but induces vascular disorders and degenerated hepatocytes, disturbed ultrastructure and organization of cells. Pb causes most severe changes, altering all measurables. H increases ATPase and SDH. N increases ATPase and SDH. V + Pb cause large changes, harmful to ultrastructure, mitochondria, and accounts for disturbed energy supply and use in liver, synergy. V+N give big changes in all factors x SDH.

**Key Words:** vibration, noise, heat, lead, combined stresses, liver pathology, energy metabolism, SDH, LDH, ATPase, interactive responses
In laboratory experiments examining the role of endorphins in hot and cold acclimatization, rats (ME SD) were exposed to: COLD and HEAT 40°C and 38°C for 1, 4, 12, 24, 48 hr before drug administrations; and NALOXONE HCl or NALTREXONE HCl (N) (narcotic antagonists), 10 mg/kg sc. N altered temperature responses to rats acutely exposed to cold or heat. Tcore dropped in cold and rose in heat. These Ns may block brain endorphins and ability to respond homeostatically to thermal stresses.

heat, cold, naloxone, naltrexone, combined stresses, thermoregulation, endorphins, narcotic antagonists, interactive responses
On the Combined Effect of Tritium Oxide, Noise, and Heat on Rats (Rus)

Tsapkov MM, Kalistratova VS, Tishchenko GS

Unnamed site, USSR

1982

3P 10R

Radiobiol (USSR) (2);22:275-277

In laboratory experiments, rats (F, random bred) were exposed to: TRITIUM OXIDE (T\textsubscript{2}O) 22.\textsubscript{MBq}/g, IP 1 time with dose 10 X max permissible level; SOUND, at 100-103 db (freq not avail) 3 hr/day for 60 days; and HEAT, 40\textdegree{} C 2 hr/day, for 60 days. Treatments included: T\textsubscript{2}O, T\textsubscript{2}O + S, T\textsubscript{2}O + H, T\textsubscript{2}O + S + H. T\textsubscript{2}O alone made no change in liver glycogen or serum cholinesterase. T\textsubscript{2}O + S caused decrease of serum cholinesterase by day 14, and glycogen content of liver. T\textsubscript{2}O + H or T\textsubscript{2}O + S + H increased liver glycogen. No other data are available.

tritium oxide, sound, heat, combined stresses, cholinesterase, liver glycogen, interactive responses.
This is a brief review of problems of combined stress exposures and of estimation of interacting responses. Factors mentioned include: IONIZING RADIATION; HEAT; NON-IONIZING RADIATION, including "short wave" and SHF; OZONE; CARBON MONOXIDE, OTHER TOXIC CHEMICALS, lead, chloroprene, formaldehyde. Specific events in interaction of ionizing radiation and heat, and responses in body weight, fertility are discussed; and the changes in nature of the interaction as functions of exposure, dosages, and energy of radiation are considered.

**Key Words**
- ionizing radiation, non-ionizing radiation, heat, toxic chemicals, combined stresses, interactive responses
In laboratory experiments mice, and rats (for excretion studies only) were exposed to: LEAD acetate, acute doses 2.2-4 mg Pb per 20 g mouse, ip or iv; or chronic doses 0.2-0.6 mg/20 g 5x/wk ip. HEAT stress, to 95°F was also used. Treatments were: 3-5 days in temp chamber at selected level, then Pb injection; or acclimatization at one temp in chamber for varying periods, Pb dose, then new temp exposure; or chronic Pb dose at 70°F then exposure to chamber temp stresses; or high temperature and dehydration (water intake restriction 3 days to 12% loss), then at high temp Pb given. Pb IP mortality has higher with heat than normal temp. There was no acclimatization with longer heat exposure. In chronic exposures, heat kills faster, high Rel Hum has no effect. Dehydration facilitates effects. Heat increases susceptibility to Pb by any route. In heat, less Pb is excreted in urine.
This surveys briefly the following topics: Metabolism of Pb, oral intake, distribution in rbc, liver, etc., excretion; Toxic effects of Pb; Factors influencing susceptibility to Pb toxicity including age, season, Ca, Pa, Fe deficiency, diet, vitamin D, protein intake, ascorbic acid, nicotinic acid, alcohol, other metals, coexistent disease, Hb anomalies, and certain metal-metal synergies.
The principal topics discussed are:

- Lead in the Environment, its sources, ecodiagrams.
- Pb Balance and Retention, Body Burden: quantitative aspects, routes of absorption and excretion; GI, pulmonary, kidney, blood content.
- Cell Response to Pb: intranuclear inclusions, mitochondrial effects, protein synthesis, cytogenetic effects.
- Neuropathology: encephalopathy, peripheral neuropathy, neurological sequel of intoxication, subclinical and asymptomatic events.
- Hematology: RBC morphology, functional effects on RBC, hemolytic effects, inhibition of heme synthesis.
- Renal: human nephropathies, experimental nephropathy.
- Effects on Other Organ Systems: reproductive, endocrine, immune.
- Factors altering dose-response susceptibility: age, season, Ca and P, protein in diet, vitamins, alcohol, Fe deficiency, synergism with metals (Cd, Hg, Zn, Al).

Key Words:

- lead, toxicology, neuropathology, hematology, metal antagonism, metabolism, nuclear inclusion bodies, interactive responses, body burden.
METALS

COMBINED STRESS EXTRACTS
**Effect of Cycloheximide on Temperature Regulation in Rats**

In laboratory experiments, rats (36 F S-D) were given CYCLOHEXIMIDE (a protein inhibitor) at 5 mg/Kg IP; and also were exposed to COLD and HEAT, at 15°C, 25°C, and 34°C, in a variety of treatment and combinations. CH caused a drop in core temp at all 3 ambient temperatures. CH also depressed oxygen consumption, but a drop in colonic temp during heat exposures did not prevent hyperthermia symptoms from appearing. There was a general effect on thermoregulation, with greatest decrease in core temp at 15°C. CH reduced ability to increase oxygen use in the cold.

**Key Words**
cycloheximide, cold, heat, combined stresses, thermoregulation, hypothalamic inhibition, hyperthermia, metabolism, thermogenesis, interactive responses
**EXTRACT**

In laboratory experiments, rats (M, random-bred) were exposed to: COLD, at 70°C, water immersion; and CHOLINOMIMETIC, other drugs, including nicotine (4 mg/kg), methacine (20 mg/kg) + proserine (0.45 mg/kg), methacine (20 mg/kg) + arecoline (20 mg/kg), or pilocarpine (25 mg/kg) all given IP. Trect defined for mild hypothermia was 33°C, for moderate 26°C and for deep 19°C. All drugs given decreased rate of development of hypothermia (RDH), in various levels of effect. A variety of differential effects were seen of drug actions on RDH and level of hypothermia. A drop of RDH in mild HT and RDH rise during deep HT may be associated with reversion of sensitivity of cholinergic receptors to acetylcholine, so with antihypothermic effects of cholinomimetics during hypothermia, compared with hypothermic effects during normothermia.

**KEY WORDS**
cold, cholinomimetic drugs, combined stresses, hypothermia, nicotine, arecoline, methacine, proserine, pilocarpine, interactive responses

**NOTES**
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<td>Five-thio-d-glucose, Hypothermic Responses in Mice</td>
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In laboratory experiments, mice were exposed to:
5-THIO-D-GLUCOSE at 20 mg IP (also 100 ug into cerebral ventricles or COLD, at 40 C and 220 C. After the drug, at 220 C there was a marked hypothermic response, not normalized after 4 hr. Rectal temperature dropped, in a dose-dependent way; after 30 min cold exposure enhanced the drop, and hypothermia led some to death. With the hypothermia caused by 5TG comes a central and peripheral 02 metabolism, along with circulating hyperglycemia.

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DD FORM 1 JAN 73 1473 (MOD.)
In laboratory experiments, rats were kept in chamber at 21°C for 1 wk before exposure to: COLD and HEAT, at 4°C, 10°C, 17°C, and 31°C; or given L-TRYPTOPHAN, at 200 or 600 mg/Kg IP, in various combinations. There was a rapid hypothermic response to tryptophan, generally highly chemospecific, with toxic effects on organs of heat production, also non-specific effects on vessels. At 4°C, the drug inhibits the increased heat production necessary to maintain body temperature. There was no effect on oxygen consumption at 31°C nor effect on glucose levels.

**KEY WORDS**
heat, cold, l-tryptophan, combined stresses, hypothermia, thermogenesis, metabolism, interactive responses
In laboratory experiments, rats (M Charles River) had hypothermia preinduced with 5-THIO-D-GLUCOSE, at 10 mg in saline iv (incomplete data). They were kept in COLD at 4°C, restrained. Trect fell to 29-30°C. They were then moved to HEAT, 35°C environment, and given EXERCISE on a treadmill to hyperthermic exhaustion (Trect of 41.5-43°C). The hypothermia lengthened the time to hyperthermic exhaustion; it improves endurance, but homeostatic mechanisms bring the Trect back. The 5TG also induced a hyperglycemia, which reverted to control levels after heat stress.
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<td>In laboratory experiments, mice were exposed to: X-RADIATION, 300 Kvp, at 265 rad/min, total doses of 50, 100, 200 rad, to thorax (with rest of body shielded to 1% dose level); and BUTYLATED HYDROXYTOLUENE (BHT), at 300, 400 mg/kg IP. When BHT is given alone, 2-4 days later there is extensive proliferation of Type II alveolar cells; 2 wks later lung collagen (hydroxyproline meast) has increased, with response BHT dose-dependent. BHT + X-rays has a synergistic effect, yielding much more collagen (hydroxyproline) in alveolar septa than either treatment alone. If given x-rays 6 days post BHT the lung collagen is not increased. Fibrosis develops when lung is damaged by a blood borne agent, (such as BHT, silica dust, 95% O2) and radiation given when these events compromise re-epithelialization. No fibrosis change occurs from x-rays during proliferation of capillary endothelial cells or interstitial cells.</td>
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Microwave Radiation and Chlordiazepoxide
Synergistic Effect on Fixed-Interval Behavior

In laboratory experiments, rats maintained at 23°C were exposed to: CHLORDIAZEPOXIDE (C), 1-40 mg/Kg IP in saline 30 min before radiation, and: MICROWAVE RADIATION 2.45 GHz, 1 mW/cm², pulsed, rep freq 500 Hz, pulse width 2 usec for 30 min. A fixed interval reinforcement schedule (FI) was used, with lever pressing for pellets, done for 1 hr immediately after radiation, with 3 replicates/dose. With C alone FI increases with dose. Effects of C are modified by MR. Brief exposure to MR acts synergistically with C, in effects on behavior, by unknown non-thermal mechanism.

KEY WORDS
chlordiazepoxide, microwave radiation, combined stresses, operant conditioning, interactive responses
A Means of Quantitative Assessment of the Joint and Complex Action on the Body of Chemical and Physical Environmental Factors (Rus)

This methods report briefly discusses probit analyses of quantitative effects of combined exposures to two or more stressors, physical or chemical, administered by diverse routes. A modification of Finney's method is discussed. This allows calculation of combined additive effects, based on % of LD₅₀ for example, and comparison with actual data to determine whether synergy or antagonism of effects are present. Specific examples using marker enzymes are considered.

probit analyses, Finney's method, additive effects, combined stresses, synergism, antagonism, interactive responses.
In laboratory experiments briefly described, mice (400 M albino) were exposed to: DIBUTYLPHENYLPHOSPHATE (DPP) (dose not available) applied to intact skin of tail for 0.5, 1.0, 2.0, 3.0 hr; also MICROWAVE RADIATION, 2,400 MHZ, 800 mW/cm², for 35 sec (probably whole body). DPP and MR had an additive effect: inhibition of blood cholinesterase within 2 wk after joint exposures and decrease in survival rate in first 8 hr after MR exposure depended on the duration of exposure to DPP. Empirical exponential equations are set down for lethality and cholinesterase change.

**KEY WORDS**
dibutylphenylphosphate, microwave radiation, combined stresses, DPP, cholinesterase, radiation biology, interactive responses
In laboratory experiments, mice (C57B1/6) and rats (albino) were exposed to: RADIOPROTECTIVE AGENTS, including Merkamine, and Ethylthiuronium; and RADIOSENSITIZING AGENTS, including colcemide, diethylether of 2-methylthiasolidine-2,4-dicarboxylic acid; all agents given IP 15 min prior to irradiation at equitoxic LD$_{50}$ doses. Also given was GAMMA RADIATION, from $^{137}$Cs at 90 R/min for totals of 600-1,000 R. Measurements, besides survival, included: bone marrow karyocyte count, peripheral wbc count, and mitotic activity in crypts of small intestine. The radiomodifying effect of the agents depended on the severity and rate of recovery from radiation injuries. Karyocyte count was the most sensitive index, and correlated with nucleic acid content in peripheral leukocytes. Agents inducing lesions in radiosensitive tissues increase LD$_{50}$ up to 80R. Some agents which briefly inhibit metabolism, reduce LD$_{50}$ to 100-200R.
**Nutritional Factors and Susceptibility to Lead Toxicity**

In laboratory experiments rats were exposed to: LEAD at 200 µg/cc in drinking water for 10 wks; CALCIUM, intake reduced to 20% of recommended; IRON intake reduced, either 5 or 25 ppm. Various combinations were given in diet and drinking water for 10 wks. Blood Pb conc rises when Ca is low. Low diet intakes (20% of recommended) + Ca or Fe increase the toxicity of Pb. Pb at 12 µg/cc in water on 20% Ca in diet has same effects as 200 µg/cc in water when normal Ca is in diet. Max dose of Pb for 10 wk not impairing heme synthesis in rat is 200 µg Pb/cc. Susceptibility to Pb toxicity is affected by age, season (UV, body temperature, dehydration), Ca, P, vitamin D, dietary protein, ascorbic acid, nicotinic acid, alcohol, other heavy metals.

**KEY WORDS**

lead, undernutrition, combined stresses, diet, toxicity, metabolism, heme synthesis, interactive responses
In laboratory experiments rats (160 Holzman, 15 wk) were exposed to: LEAD acetate at 1 mg Pb/cc in drinking water for 5 wks; and various diets: normal protein diet; or low-protein diet (with 8% casein and 1% alanine) (LP); or LP + 1% cystine; or LP + 1% methionine. Measurements were made of: decrease in growth rate, reduced food use, increased urinary del-amino-levulinic acid, Pb induced anemia (reduced Hb, RBC, hematocrit). The LP diet was associated with severe toxicity and high blood Pb (369 ug %). if methionine or cystine replaced the alanine, this reduced Pb toxicity and blood Pb (without change in tissue Pb concentration). On normal protein diet (27% casein) although there are many signs of Pb toxicity, blood Pb conc is only 1/6 that on low protein diet, and there is no drop in kidney or liver Pb, but there is a rise in bone Pb. On these diets, blood Pb did not mirror tissue Pb or Pb toxicity or Pb exposure: blood Pb as indicator is fallacious.
Experimental Enhancement of Lead Toxicity by Low Dietary Calcium

In laboratory experiments Rats (30 SD albino) were exposed to: LEAD at 200 ppm in drinking water for 10 wk (a subclinical toxic level when given with normal diet); CALCIUM gluconate, at 0.1% (deficiency level) or 0.7% (normal dietary level) in diet. These were given in various combinations for 10 wks. The lower Ca level would not be unreasonable in urban poor, and yields increased absorption and urinary excretion of Pb, and increased Pb levels in blood, tissue, bone. There are also more frequent and large intranuclear inclusion bodies, changes in kidney size and tubule cells, etc.

lead, calcium, combined stresses, diet, anemia, toxicity, del-aminolevulinic acid, intranuclear inclusion bodies, interactive responses
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**EXTRACT**

In laboratory experiments rats (74 M SD albino) were exposed to: LEAD acetate at 3-200 ug/cc in drinking water; and CALCIUM gluconate at 0.1% (deficiency) and 0.7% (normal level) given in diet. Various single and combined doses were given with water and diet for 10 wk, then tissue analyses were made.

Susceptibility to Pb effects increased, several multiples, by low Ca (0.1%) equivalent to Pb rise of 6-26 ug/cc in water. Low Ca enhances effects of low levels of Pb, as shown by intranuclear inclusion bodies (Pb-protein complexes), femoral and kidney Pb and del-aminolevulinic acid.

**KEY WORDS**

lead, calcium, combined stress, diet, toxicity, nuclear inclusion lead-protein complexes, interactive responses

**NOTES**

DD FORM 1 JAN 73 1473 (MOD.)
### Extract

In laboratory experiments rats (M, SD, weanlings) were exposed to: COPPER at 0.5-8.5 ppm, ZINC at 20-140 ppm, LEAD 0-500 ppm, added to drinking water; and IRON at 40 ppm added to feed diets. The basic diet with these selected supplements was provided for 12 wks. Dietary Fe + Cu showed the biggest effects, with inverse relation to Pb absorption (measured by Pb in RBC and kidney). Cu levels in kidney drop with lowered Fe in diet, and are depressed by Pb. Pb interfered with hematopoiesis when diet Cu and/or Fe are low. The effect was greater with Cu + Fe. When Cu and Fe are low, there is an increase in RBC Pb. Some toxic effects of Pb are reduced if Cu + Fe + Zn are adequate.

### Key Words

copper, iron, lead, combined stresses, diet, metabolism, toxicity, hemopoiesis, interactive responses
In laboratory experiments rats (31 M albino, young) were exposed to: COPPER chloride at 1, 5, or 20 ppm (5 is the current diet recommended level for rats); also LEAD acetate from 0-200 ppm. Either or both were given in basic diet. Dietary Cu increased the severity of Pb toxicity. Increases occurred in Pb in kidney, urinary del-aminolevulinic acid, and Cu in liver rose. The interactive effect got stronger with rise in dietary Cu. Other data are presented on interactive effects.
Some special problems in this field are highlighted. Conflicts of data relate to: types of studies, route of Pb and other exposure, mode and content of feeding. Calcium and Lead interactions include: Ca effects on Pb absorption and excretion, on tissue and organ distribution, Ca deficiency and Vitamin D events; Pb influence on Ca metabolism, undernutrition and the childhood Pb burden, and various clinical correlations. Iron and Lead interactions include: Fe effects on Pb absorption and excretion, tissue and organ distribution, various Pb effects on Fe, and clinical correlations. Many of these topics are discussed at length.

lead, iron, combined stresses, diet, metabolism, interactive responses
**The Influence of Iron Deficiency on Tissue Content and Toxicity of Ingested Lead in the Rat**

**In laboratory experiments rats (33 M SD albino) were exposed to:**

- **LEAD** at 200 μg/cc (a subtoxic dose); then one group received **IRON** as ferrous sulfate at 25 ppm in purified diet also containing Calcium and Phosphorus; the second group received Fe sulfate at 5 ppm (low level). Fe deficiency increased the retention of Pb in liver, kidney, bone and soft tissue; and there was increase of Pb urine excretion and of D-aminolevulinic acid in blood. Fe deficiency also increased, in other studies, the absorption of Mn, Co, and Zn. The Fe deficiency and Pb response are considered synergistic effects.

**Key Words**

- iron, lead, combined stresses, toxicity, diet, del-aminolevulinic acid, interactive responses
In laboratory experiments hamsters (pregnant, on day 8, where major organ systems are established in a 24 hr period) were exposed to: CADMIUM sulfate at 2 mg/Kg IV; also LEAD acetate at 50 mg/Kg IV by injection of the mother with one or both. Cd alone caused anterior malformations. Pb alone caused tail malformations, as seen in day 13 fetal hamster. The anterior Cd effects were reduced in the presence of Pb. Also the posterior malformations from Pb were potentiated by Cd. Speculations concern whether these are direct effect on embryonic tissues, or a block of some essential placental transfer, or some induced defect in metabolism which affects embryonic tissues. Cd and Pb may interact additively on metalloenzymes in altering the tail bud.
In occupational observations workers (90 M, 60 F) in storage battery, nickel-cadmium chemical and electronic factories, were exposed to CADMIUM dust, approx 100 μg/m³ (77 workers), with the other workers (73) selected as controls, without these exposures. No data were provided, but the LEAD and NICKEL exposures are considered to be concurrent. Measurements were made of ALA-D (RBC), and U-ALA, Pb in blood, Pb in urine, Cd in blood, Cd in urine. An inverse relation was found between ALA-D and B-Pb or U-Pb. ALA-D activity was not correlated with B-Cd and the potential effect of Cd on ALA-D in the general population was considered negligible compared with Pb. Cd had no significant effect to depress ALA-D in RBC. But depression of ALA-D in RBC was regarded as a sensitive and specific early warning of Pb in blood. This was the extent of reporting on present work.

**KEY WORDS**

lead, cadmium, combined stresses, battery industry, dust, aminolevulinate dehydratase, electrical industry, nickel, hematology, interactive responses
In laboratory experiments rats (M, SD, young) were exposed to: zinc carbonate at 8, 35, 200 ppm; also lead acetate at 50, 200 ppm with one or both added at various doses to semi-purified diet over 7 wks. Another series was fed low Zn basal diet for days 1-7. At day 5, some got Zn IP at 100 ug dose, repeated on day 6, with fasting till day 7. On day 7 Pb 3mg was given in diet, and on day 8 Zn was given. Large dietary loading with Zn (200 ppm) reduced many toxic effects of Pb, in a manner similar to 50 ppm dose. Increase of dietary Zn decreases Pb toxicity, drops Pb levels in blood, liver, kidneys, and bone, reduces excretion of U-ALA, and free RBC porphyrin. Injection of Zn gives no protection against Pb toxicity; major action is by inhibiting Pb absorption at intestinal level. Pb and Zn compete for binding sites on metallothionein enzymes.

**Key Words**
- zinc, lead, combined stresses, diet, toxicity, metallothionein, porphyrins, interactive responses
**Influence of Dietary Zinc on Lead Toxicity in Rats**

**Authors:** El-Gazzar RM, Finelli VN, Boiano J, Petering HG

**Performing Organization:**
Univ Cincinn Dept Envir Hlth, Kettering Lab, OH; EGYPT: High Inst Pub Hlth Alexandria

**Publication:**
Toxicol Lett 1978;2:227-234

**Extract:**
In laboratory experiments rats (28 M weanlings) were exposed to: zinc acetate at 5, 50 ug/cc in dietary drink; also lead acetate, at 100 ug/cc in dietary drink. One or both of these were given in various combinations together with semi-purified diet, for over 140 days. Rats on low Zn doses started with slow growth but caught up. Pb raised urine del-aminolevulinic acid, also increased Zn protoporphyrin. High diet Zn reduces Pb levels in various tissues, and lowers U-ALA. Pb reduces Zn levels in plasma, liver, tibia. RBC Zn protoporphyrin (ZPP) is affected by diet Zn also Pb. RBC Pb is highly correlated with ALA, ZPP, and U-ALA. Zn then has a protective role in Pb toxicity. It is not only an antagonist at intestinal absorption sites, but also in tissue at enzyme levels.

**Key Words:**
zinc, lead, combined stresses, toxicity, diet, protoporphyrin, del-aminolevulinic acid, interactive responses
In laboratory experiments rabbits (32, 7F, 25M, white furred breed, ages 1-2 yr) were exposed to: ZINC sulfate at 22.5 mg Zn/cc given sc; LEAD acetate at 28.0 mg Pb/cc given sc. Treatments were: Zn at 63 mg/Kg, then 202 mg/Kg; Pb at 25 mg/Kg, then Zn 200 mg/Kg; or Zn 50 mg/Kg, then Pb 18 mg/Kg. Del-aminolevulinic acid dehydratase is a sulfhydryl enzyme involved in biosynthesis of heme (catalyzes 2 molecules of D-ALA condensing to 1 of porphobilinogen. Activity is inhibited by heavy metals. Zn activated ALAD in vivo, and almost completely inhibited effect of Pb. Pb dose is first followed by suppression of ALAD. ALAD in rbc and Zn in plasma are linked, but there is no correlation between ALAD and Zn in rbc. Zn and Pb have an antagonistic effect on ALAD. Normal ALAD rbc is higher in rabbits than humans, and there are differences in amounts and sites of binding of Pb and Zn in blood.
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<td>14. PUBLICATION</td>
<td>Int Arch Occup Environ Health 1979;42:341-348</td>
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<td>16. EXTRACT</td>
<td>In occupation observations in the LEAD and ZINC metals industries among workers (97) with 1-9 yr contact, measurements of Pb in blood av 40-100 ug/100 cc. del-aminolevulinic acid (ALA) was over 5 mg/dm³ in 89 subjects. Mixed exposures to Pb + Zn reduced U-ALA, an antagonist effect. Evaluation of hazards of Pb + Zn must consider Zn serum level and ALA; Zn is essential in ALA biosynthesis.</td>
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<td>17. KEYWORDS</td>
<td>lead, zinc, combined stresses, del-aminolevulinic acid, toxicity, lead-zinc industry, interactive responses</td>
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**DD FORM 1 JAN 73 1473 (MOD.)**
### Effect of Cadmium on Dose-Response Relationships of Zinc in Rats

In laboratory experiments, rats (M SD) were exposed to: ZINC Acetate at 0.03, 0.122, 0.488 mM and CADMIUM, both orally in semi purified diet and drinking water (no other data). Zn deficiency in normal rats causes rapid decrease in growth or loss in weight. When deficient rats are given Zn supplement, immediate increase in growth occurs; linear responses to log doses are shown for growth, wbc, Hb, and rectal Temp. Cd given lowered Trect and altered normal response to Zn in growth, and blood conc of Zn. There is a competitive antagonism of Cd and Zn. Cd also is localized in liver and kidney, but not in testes.

**Key Words:**
cadmium, zinc, combined effects, growth, toxicity, diet, deficiency syndromes, interactive responses
In laboratory studies, rats (60 M weanling) were exposed to: ZINC acetate, 30.5 uM 74 days, then 122 uM in 78 days, then 488 uM 78 days, in drinking water with semipurified diet; or Zinc Acetate at 30.5 uM for days 28-56 + CADMIUM Chloride at 30.5 uM on days 28-74. Toxic symptoms in Cd (growth reduction and gross pathology) were related to Zn/Cd ratio. Some of Cd toxicity rests in interference with Zn metabolism. Cd changes Zn and Cu in liver and kidney. Zn alters Cu levels in liver and kidney. Cd reverse these effects like an antimetabolite for Zn. Cd localizes in liver and kidney, but not in testes. After Zn deficient diet, rats respond fast and directly in growth to Zn in water. If Cd is given at Zn/Cd 1:1 blood Zn and Cu go up, but no effect if Zn/Cd 4:1. Zn deficiency pathology is enhanced by concurrent Cd. Other findings are reported here.

**Key Words**
- zinc, cadmium, combined stresses, metabolism, diet, toxicity, interactive responses
Effectiveness of Selenium and Zinc in Protecting against Cadmium-Induced Injury of the Rat Testis

Mason KE, Young JO, Brown JE

Univ Rochester Schl Med & Dent NY

Anat Reg 1964 (Feb);148:309 (abstract)

In laboratory experiments, rats were exposed to: simultaneous doses of ZINC sq, up to 160X that of CADMIUM also administered, with no propective effect against testis injury caused by Cd. But if Zn 30X that of Cd is given in 1 dose 1 day before Cd or distributed 3-6 days before, some protection is provided by the Zn against Cd action (Timing differences relate to low absorption of Zn). SELENIUM compounds at 2X Cd dose given simultaneously with Cd are protective against Cd damage, and are effective if given up to 4 hr before Cd. Se 3X Cd is effective up to 6 days before Cd. When Cd protection is not effective testis damage include infarcts in efferent ductules and proximal segments of the epididymis, bilaterally.

zinc, cadmium, selenium, combined stresses, protective agents, toxicity, testis pathology, interactive responses
Properties of the Cadmium and Selenium Complex Formed in Rat Plasma in Vivo and in Vitro

In laboratory experiments rats (M SD) were given MERCURY as HgCl\textsubscript{2} or CH\textsubscript{3}HgCl labelled with \textsuperscript{203}Hg; also CADMIUM chloride labelled with \textsuperscript{109}Cd; also SELENIUM as Na\textsubscript{2}SeO\textsubscript{3} labelled with \textsuperscript{75}Se, all given simultaneously sq (no other data). The rats were then exsanguinated and studied. There was evidence of Cd-Se complexes in plasma in vivo and in vitro. The stability of these complexes depends on integrity of protein components in plasma. Metabolism may produce H\textsubscript{2}Se or similarly reduced selenides. Other data on Hg and its formation of protein complexes and various protective combinations are discussed.

Key Words: cadmium, selenium, mercury, methylmercury, protein complexes, toxicity, interactive responses
**Additive Statistical Effects of Cadmium and Lead on Heart-Related Disease in a North Carolina Autopsy Series**

In an epidemiological study of associations of heart-related mortality with tissue CADMIUM and LEAD in softwater leached from the soil in 92 sample areas of N Carolina: Cd and Pb levels, and their relation with tissue Cd (eg liver) and Pb (eg aorta) showed sufficient correlation with heart related deaths to allow prediction of cause of death correctly in 80% of deaths sampled. Cd and Pb act additively on the same targets. Mentioned but not analyzed are nutrient protective effects of Ca, Se; Pb in "moonshine" and Cd in cigarettes, and the specific mechanisms of damage in the CV system. Cd is in the soil available to food and fodder if soil is acidic, and plumbosolvency in Pb containing pipes contributes to the soft water Pb.

**KEY WORDS**
cadmium, lead, combined stresses, epidemiology, heart disease, mortality, water hardness, interactive responses
### Extract

In laboratory studies rats (Long-Evans strain) were exposed to cadmium in various treatments: 1. Cd acetate at 5 ug/cc in drinking water daily to 400 days (at which time 11 of 22 showed systolic blood pressures in hypertensive range), 9 were given zinc disodium Zn CDTA IP 27-36 mg/Kg, and BP measurements made to 21 wk. 2. 10 F 120 day given Cd at 2 mg/Kg IP 1x, then 1 mg/Kg 3 wk later; 10/10 had HBP, then 8 given Disod.Zn CDTA chelator IP 1x, BP measd to 48 hr later, if still HBP 1-2 more doses. 3. 18 older rats given 1 mg/Kg CdAc, repeated 1 wk later. Survivors with HBP given CDTA at wk 3 and killed wk 4. 4. Cd 1.5 mg/Kg IP 1 wk later ZnCDTA IP, studied 1 day later. Hypertension caused by CdAc at 5 ug/Kg 400 days in water or IP 1.5-2 mg/Kg. Treatment with ZnCDTA at 9.1 mg caused hypertension to regress to normal levels without toxic effects. Of 8 given Cd, after ZnCDTA 4 were normal for 2 mo, 4 normal for 5 mo.

### Keywords

cadmium, zinc, combined stresses, hypertension, chelates, Zn-cyclohexan-diamine-tetraacetic acid, interactive responses, protective effects

### Notes
Combined Effect of Carbon Monoxide and Metallic Mercury Vapors on the Organism of Test Animals (Rus)

Shulga TM, Bazina AA

Med Instit, Smolensk USSR

Gig sanit (USSR) 1975 (1); 59-63

In laboratory experiments rats (M random bred) were exposed to: CARBON MONOXIDE at 18.87 mg/m³; or MERCURY at 0.014 mg/m³; or CO 18.83 mg/m³ + Hg vapor 0.009 mg/m³ inhalation exposure for 8 hr/day, 5 days/wk, for 4.5 mo. Measurements were made of coproporphyrin excretion, oxygen consumption, blood pressure rise, rbc and wbc count, cholinesterase activity, organ weight, adrenal vitamin C content, and neural thresholds. Single substance doses were close to local MPC and had toxic effects. CO + Hg showed additive effects. No other data were available.

carbon monoxide, mercury, combined stresses, toxicity, coproporphyrin, cholinesterase, metabolism, interactive responses
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<td>Oreg State Univ Schl Vet Med, Envir Hlth Sci Ctr, Corvallis</td>
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<td>In laboratory studies mice (384 M) were exposed to: METHYLMERCURY Chloride at 1, 5, or 10 ppm in chow diet; SELENIUM as sodium selenite, 6 ppm in water; given alone or together for 10 wks. MeHg + Se causes significant increase in antibody synthesis, a response greater than Se alone, and MeHg alone depresses synthesis. Hg conc in kidney is higher when MeHg + Se are given vs MeHg alone. The synergistic increase in antibody producing cells involves primary and secondary immune responses. Effect of such combinations can only established empirically at the present state of the art.</td>
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**Effect of Selenite on the Toxicity of Dietary Methylmercury and Mercuric Chloride in the Rat**

In laboratory experiments rats (72 SD) were exposed to: mercury as Methylmercury chloride at 10, 20, 40 ppm in feed; or given as HgCl₂ at 20 or 40-400 ppm in diet; also selenium as sodium selenite at 5 ppm. Treatment was 26 days, first on diet containing Hg (in selected form) alone or with Se (after basal diet for 1 wk) then back to basal to day 74. Se increases Hg retention in liver and spleen, and protects against mortality, increase, growth depression, and neurotoxicity. MeHg is more toxic than equal doses of inorganic Hg. Se metabolism may include formation of dimethyl selenide.

**KEY WORDS**

mercury, selenium, combined stresses, methylmercury, metabolism, toxicity, diet, protective effects, interactive responses
Effect of Cystine, Selenium, and Fish Protein on the Toxicity and Metabolism of Methylmercury in Rats

Stillings BR, Lagally H, Bauersfeld P Soares J

US NOAA Nat Marine Fisheries Svc, College Park Fishery Prods Technol Lab MD

Toxicol Appl Pharmacol 1974;30:243-254

In laboratory experiments rats (74 M & F weanling) were exposed to: MERCURY as Methylmercury chloride at 25 ppm in diet; L-CYSTINE at 0.4%; or SELENIUM as sodium selenite at 0.6 ppm. Treatments were: MeHg; or MeHg + Se; or MeHg + L-C; some in combinations with 10% fish protein diet; all diets for 10 wks.

In diets with 25 ppm Hg and 10% protein, cystine reduces toxicity, and Se offers greater reduction. Cystine + Se yield an additive greater effect in increased growth and survival time with MeHg. Toxicity of MeHg is reduced if fish protein replaces casein, and 20% protein is better than 10% in this regard. Inhibition of MeHg toxicity is not related to elimination (actually more Hg may be retained). An artefact to be avoided in such studies is that commercial cystine contains up to 2% Se.

mercury, selenium, l-cystine, fish protein, combined stresses, diet, toxicity, methylmercury, metabolism, interactive responses
In a brief survey of trace element interaction these topics are discussed: direct chemical reactions between these elements and their compounds eg in vitro; metabolic changes induced by prior dose of SELENIUM, modifying dose-effect forms for other elements by interaction at physiological levels, eg at Se intake locales; specific protective effects of Se injections in animals exposed to lethal inhalation doses of Cd; Se protection against organic and inorganic forms of Hg; and other related topics.

**18. KEY WORDS**

selenium, mercury, cadmium, combined stresses, metabolism, toxicity, protective effects, interactive responses
**Extract**

In laboratory experiments rats (M Long-Evans) were exposed to: SELENIUM as sodium selenate 0.01 mmol/Kg sc; also MERCURY as 203HgCl2 (104 uCi) at 0.01 mmol/Kg. In the treatments, all were given sc: Hg alone, or Se 30 min before Hg. Animals were prepared for analyses 1 hr later. Se decreases Hg toxicity, associated with a redistribution of Hg, which is increased in blood and testes and reduced in kidney. This Se driven diversion to less critical tissue components also occurs with Cd. Also here, the Hg in the "soluble fraction" (a major subcell Hg binding component) is diverted from low mol wt proteins to large mol wt proteins as in liver, testes, kidney.

**Key Words**
mercury, selenium, combined stresses, toxicity, tissue dose, pathology, interactive response
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<td>(Moscow) Regional Clin Res Inst at Vladimirskogo, USSR</td>
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<td>In occupational observation and clinical study, workers with ceramic dyes (90, 86 !, 4 F, ages 25-50 yr) were exposed to: LEAD at 0.17-0.66 mg/m³, SELENIUM at 0.05-2.4 mg/m³, and COBALT at 0.4-0.6 mg/m³, each in aerosol form. One group (41) were exposed to Pb alone, a second group (49) encountered Pb + Se + Co. Studies were made of rbc count, urine coproporphyrin, and del-aminolevulinic acid. In the combined exposure group, the toxic effects of Pb were more pronounced, with lower Hb, increased count of basophilic granular rbc, and increased excretion of ALA and CP. Under industrial conditions, Se in the concentrations given here, cannot protect from Pb toxicity.</td>
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**DD FORM 1 JAN 73 1473 (MOD.)**
In laboratory studies rats were exposed to LEAD as Lead naphthenate, (used in lube oils and greases) 80-200 mg Pb/Kg in 5% ether, dripped onto skin, for 8 wks; and SELENIUM as Sodium selenite, at 5, 10, 15 ppm Se in drinking water (above the known 3 ppm Se in water chronic toxicity threshold). The two disparate routes of administration were selected to avoid interaction before body uptake. Se or Pb alone reduced growth rate and feeding. With Se + Pb growth rate and food consumption approached normal, as were del-aminolevulinic acid (ALA) in blood, liver, and kidney, also liver cytochrome P-450. ALA or P-450 were depressed with Se or Pb alone. The antagonism of toxic effects by Se with Pb bears little relation to findings of high levels of the metals in the organs. Pb may also form complexes with Se, like PbSeO3, and Se enters brains in combined form, and may offset possible damage to blood brain barrier by Pb.

**Key Words**
selenium, lead, combined stresses, diet, lubricating oils, lead naphthenate, del-aminolevulinic acid, interactive responses
In laboratory experiments, hamsters (pregnant, on day 8, where major organ systems are established in a 24 hr period) were exposed to: CADMIUM Sulfate at 2 mg/Kg IV; or ZINC sulfate at 2 mg/Kg IV, separately or in combination. Cd induced facial abnormalities. Simultaneous administration of Zn prevented Cd teratogenicity. Cd given 12 hr after Zn failed to protect. Cd may induce inhibition of sulfhydryl enzymes and succinoxidase.

KEY WORDS

cadmium, zinc, combined stresses, teratogenesis, toxicity, interactive responses
# Arsenic Exposure and Mortality: A Case-Referent Study from a Swedish Copper Smelter

Axelson O, Dahlgren E, Jansson CD, Rehnlund SO

This case-control epidemiological study of workers in copper smelting, done with aid of Boliden Mettall Skelleftehamn, used data from local registries on 369 deaths, av ages 60-76 yr. Special attention was paid to exposure to ARSENIC (trivalent), COPPER, and SULFUR DIOXIDE. Exposure estimates began with 1928 hygienic standards, and established 3 levels relative to 0.5 mg/m³ below, close, and over this level. Also taken into account was the exposure period, and its relation to latency periods for responses to emerge. Analyses considered 325 subjects, 74 controls (who died from unrelated causes), yielding 251 cases (with 10 diagnoses in 2 categories/subject). Selected cases dealt with lung tumors and bronchial cancer (lung cancer mortality was up 5X over controls, and is As dose-response related); CV disease (up 2X); leukemia, myeloma and other malignancies (increased).

arsenic, copper, combined stresses, toxicity, copper smelting, case-control studies, epidemiology, lung disease, cardiovascular disease, interactive responses.
**Extract**

Observations were made on deceased workers (40 M av 66.6 yr) at smelter in Ronnskarsverken in N. Sweden. ARSENIC and SELENIUM in lung, liver, and kidney were determined using neutron activation. There was a 7x level of As in lungs of workers compared with unexposed controls; and this As level in lung cancer was about the same in other malignancies or cardiovascular diseases of these men. In 6 who died of lung cancer there were the highest concentrations of the metals, as well as accumulations of Sb, Ln, Pb, and Cd. 15/40 died from various malignancies, 17 from CV disease, 5 from cerebrovascular events. Exposure periods av 31 yr. Arsenic kidney cortex was 5 ppb, in lung av 50 ppb, with wide variability found in normal tissues (unexposed controls). In this epidemiological study, multifactorial causes for excess mortality among smelters are examined with consideration of smoking, toxic gases, and other metals exposures.

**Key Words**

arsenic, selenium, combined stresses, smelting industry, toxicity, lung pathology, kidney diseases, epidemiology
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Arsenic and Cancer: Effects of Joint Administration of Arsenite and Selenite on the Genesis of Mammary Adenocarcinoma in Inbred Female C3H/St Mice

5. **TYPE OF REPORT & PERIOD COVERED**
Jnl article

6. **PERFORMING ORG. REPORT NUMBER**

7. **AUTHOR(A)**
Schrauzer GN, White DA, McGinness JE, Schneider CJ, Bell LJ

8. **CONTRACT OR GRANT NUMBER(S)**
G:Nat Fisheries Inst DC
G:Se-Tl Devel Assn
G:U Cal Ca Res Coord Ctee

9. **PERFORMING ORGANIZATION NAME AND ADDRESS**
Univ Cal, Revelle Coll, Dept Chem, La Jolla, CA

10. **PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS**

11. **CONTROLLING OFFICE NAME AND ADDRESS**

12. **REPORT DATE**
1978

13. **NUMBER OF PAGES AND REFS**
9P 20R

14. **PUBLICATION**
Bioinorgan Chem 1978; 9: 245-253

15. **SECURITY CLASS. (of this report)**

16. **EXTRACT**
In laboratory experiments, mice (F, inbred C3H/S+) were exposed to: ARSENIC as Sodium Arsenite at 2 ppm; or SELENIUM as Sodium Selenite at 2ppm, each or both together in drinking water (protective effects of As may not be seen if given with feed instead of water). In these cancer susceptible mice, As abolishes any anti-carcinogenic effect of Se; there is a joint increase in spontaneous mammary adenocarcinoma over each alone. As alone increases tumor growth in rats also incidence of multiple tumors. Se stimulates certain immune responses, has antimutagenic effects. It is speculated that As + Se inactivate each other by direct chemical combination in the cell.

17. **KEY WORDS**
ar senic, selenium, combined stresses, cocarcinogenesis, toxicity, adenocarcinoma, interactive responses, protective effects

18. **NOTES**
In laboratory experiments, hamsters (pregnant, on day 8, where major organ systems are established in a 24 hr period) were exposed to: HEAT at 40°C for 50, 55, 60 min to induce hyperthermia; or ARSENIC as Sodium Arsenate 10 mg/Kg (a dose at the malformation threshold) then heat at 1, 2, 3 hrs after IP injection; or Sodium Arsenate at 10 mg/Kg IP then kept in dark cabinet. As + heat are synergistic. Combinations of minimal teratogenic levels of each cause marked rises in frequency and severity of developmental malformations and in fetal resorptions. Hyperthermia of 3 or 4°C rise can induce encephalopathy in fetuses of hamsters, rats, guinea pigs. The synergy may exist because heat accelerates chemical reactions, or changes permeability of the placenta or from intrinsic mitotic sensitivity to both agents, or from all 3 mechanisms.

arsenic, hyperthermia, combined stresses, teratogenesis, toxicity, interactive responses
In laboratory experiments, hamsters (on day 8, where major organ systems are established in a 24 hr period, pregnant females) were exposed to: CADMIUM sulfate at 2 mg/Kg IV; or ARSENIC as Sodium Arsenate at 20 mg/Kg; or SELENIUM as Sodium Selenite at 2 mg/Kg. Cd is teratogenic, at the sublethal dose given 50% will be malformed. As is teratogenic, at the dose above there are major malformations. Se is not itself teratogenic, but does protect against malformations of Cd and As if Se is given at same time as either. This protection is still marked up to 30 min, then drops rapidly at 2 and 4 hr. The Se can cross the placenta, alter metabolism, and may form protective complexes, in its antagonistic effects.

**KEY WORDS**

selenium, arsenic, cadmium, combined stresses, toxicity, fetal metabolism, teratogenesis, interactive responses
In laboratory experiments, rats (40, hooded, age 4 mo) were exposed to MANGANESE Chloride at 4 mg/Kg IP 1/day x 30 days; while IMMobilized for 2 hr/day in cylindrical holders. There was no effect on CNS of handling or immobilization alone. There is no change in CNS deposition, concentration, or handling of Mn under immobilization stress. There are changes in brain tyrosine, tryptophan, dopamine, norepinephrine with combined Mn and immobilization, and the effects may be additive. No other data are available.
General Subcellular Effects of Lead, Mercury, Cadmium, and Arsenic

Each element alone interferes with normal cell replication, genetic processes, and metabolic events. LEAD has a broad spectrum of actions: intranuclear inclusions, abnormal mitoses, polyploidy, chromosome gaps; also mitochondrial swelling, changes in respiration, specific inhibitions eg of lipoic acid dehydrogenase; also endoplasmic reticulum changes, microsome enzyme activations, protein synthesis. MERCURY also causes changes in nuclei, DNA, RNA, protein synthesis, mitochondria, lysosomes, endoplasmic reticulum. CADMIUM generally affects all subcell parts. ARSENIC toxicity evaluation must consider the chemical form and oxidation state; the trivalent has the worst action, though the pentavalent form is more common.

lead, mercury, cadmium, arsenic, combined stresses, toxicity, heme synthesis, nuclear inclusions, mitochondria, microsomes, endoplasmic reticulum, interactive responses
Some observations on the Interaction of Zinc, Copper, and Iron Metabolism in Lead and Cadmium Toxicity

This surveys the effects in rats and on L cells in vitro after po administration of LEAD and CADMIUM, in normal and deficient diets, with observations on metabolism of Zinc, Copper, and Iron. Nutritional deficiencies can increase absorption and toxicity of oral Pb and Cd; and the latter can perturb metabolism of Zn, Cu, and Fe (providing some earliest signs of toxicity from Cd or Pb. Nutritional status must be considered in metals toxicity (also among industrial workers), and nutritional improvement offers a preventive role especially in trace metal intakes. Pb and Zn interact to alter del-aminolevulinic acid; Zn has a protective action on Pb absorption and biological effects. There are Pb–Fe interactions; low Cu enhances Pb absorption; Cd acts on Zn metabolism, absorbed Cd affects Cu and Fe metabolism, and none acts independently here.

lead, zinc, copper, iron, cadmium, combined stresses, toxicity, diet, metabolism, interactive responses
Observations were made on 500 Belgium women during pregnancy for exposure to LEAD, MERCURY, CADMIUM, AND CARBON MONOXIDE. Mean levels were: Pb 3.1-31 µg%, Hg 0.01-4.6ug%, Cd 0.01-1.0 ug%, and COHb 0.12-4.84 %. Factors of smoking, residence site, age, occupation, drinking were considered. No other data were given.

A variety of other problems are discussed. In humans and rats, heme biosynthesis pathway is susceptible to Pb alteration, shown by increased Free Erythrocyte Porphyrin (FEP) concentration. This response is greatest in the young, less in adult females, least in adult males. Cd proteinuria seen in workers involves changes in tubules and glomeruli. There is no synergy of Cd and Pb in this proteinuria or these kidney changes. Hg (if methylmercury) goes from mother to fetus easily, Pb less easily, Cd least easily. Sex hormone interact with FEP response in adult rats. There is discussion on protein clearance in exposures to these metals.
Experiments are described using lambs (30 M age 4 mo) exposed to: CADMIUM at 0, 5, 15, 30, 60 ppm fed in standard diet for 191 days. Tissue Cu, Zn, Fe, and Mn was measured. Cd in all tissues goes up with diet Cd; Fe in ileum goes down; liver Cu, Fe, Mn go down, and Zn rises in liver; spleen and testes Cu drops, whereas kidney Cu and Zn rise. There are specific interactions among Cd, Cu, Fe, Zn, Mn, some perhaps by direct effect of Cd on absorption, storage, excretion. Cd displaces Zn from muscle and bone. Low conc of Cd in diet alters Cu metabolism.
Limited information is provided in measurements made on workers in auto garages and repair shops, exposed in various processes to Cd, Cu, Cr, Mn, Ni, Zn, Fe, Pb, Ti, V, and others from welding fumes, paints, and organometallics in lubricants (eg Mn tricarbonyl). The report deals only with metals in the actual combined exposure environment. Measurements of these substances in the workers, along with analyses for del-aminolevulinic acid, carboxyhemoglobin and other factors, are discussed for various combinations of exposure. Comparisons of findings with calculations of approach to TLV limits, using additive interaction equations, are considered.
Factors Influencing Effects and Dose Response Relationships of Metals

This discusses interactions of a number of toxic metals, as may occur in vivo and in vitro. Modes of encounter are described, including non-interactive events, interactions of additive or synergistic or antagonistic classes. Comparisons of various animal tests, relation of metals and nutrition, influence of therapeutic drugs on metals metabolism and toxicity are considered. The relation of other chemicals to metal toxicity, changes in toxic reactions with organism age, from fetus and neonate on, and interactions with physical environmental factors are also discussed.
In a brief survey as part of a symposium on this subject, a diagram shows a large variety of possible metal-metal interactions, some competing for ligands, e.g., Cd, Zn to metallothioneins. Also discussed are absorption-facilitating complexes such as picolinic acid and Zn metabolites. Brief reference to metals discussed here and in the symposium include Mn, Co, Pb, Fe, Ni, Cr, V, F, Zn, Cu, Mo, W, As, Si, Cd, Hg, Mg, Se, and Rb. Information sources are cited on Cd, Pb, and Hg interactions with essential elements.

**KEY WORDS**

toxic elements, essential elements, combined stresses, metabolism, chemical complexes, interactive responses
MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS:1963 A
This short survey paper discusses reaction between two metals chiefly in vitro: their competition for carriers, metabolic interferences, the induction of protein binding sites, various morphologic factors, and interactive synergistic and antagonistic effects, as applicable to combined stressor studies in vivo.
In laboratory studies, rats and mice were pretreated for 2 wks either with a copper deficient diet (to deplete COPPER) or a normal diet. All were then given diets containing IRON 100 ppm, COPPER 2 ppm, ZINC 9 ppm, and CADMIUM 0 or 100 ppm in various mixes. Cd reduced wt gain and Hb, and lowered liver Fe. Pretreatment conditioned a GI tract modification related to dietary cations. When the tract is condition to normal trace levels of cations, it is able to absorb more Cd. Supplemental Cu and Zn overcame adverse effects of Cd in Cu deficient diet, but not in normal diet.

KEY WORDS
- copper, cadmium, combined stresses, zinc, iron, diet, intestinal absorption, trace metal metabolism, interactive responses
In laboratory studies, rats (120 M on casein enriched diets) were exposed to: CADMIUM chloride at 50 ppm, LEAD acetate at 200 ppm, and ARSENIC as Sodium arsenate at 50 ppm, added to diet as single or combinations of pairs or triad, for 10 wks. Cd made no change in uric acid or kidney wt or urinary porphyrins, but reduced alkaline phosphatase, Hb and Hematocrit, Fe in liver, kidney, and femur, and Zn in femur and increased rbc. Pb made no change in wt gain or feeding or alkaline phosphatase, raised uric acid, kidney wt (nuclear inclusions and mitochondrial swelling), raised U-ALA. As dropped SGOT, alk phosphatase, Hb, Ht, no change in kidney wt but swells tubule mitochondria. Cd + As drops wt gain more than each alone, Cd + Pb reduces Pb levels and tissue burden in bone and kidney and kidney nuclear inclusions. Pb + As raises further coproporphyrin levels, not uroporphyrin or ALA. Pb + Cd + As causes higher rise in rbc than each separately.

**Keywords:**
cadmium, lead, arsenic, combined stresses, diet, toxicity, heme synthesis, organ pathology, kidney intranuclear inclusions, interactive responses
Effects of Concurrent Administration of Dietary Lead, Cadmium, and Arsenic in the Rat

In laboratory studies, rats (168 M adult SD) were exposed to: CADMIUM, at 50 ppm, ARSENIC as Sodium Arsenate 50 ppm, or Lead at 200 ppm; with each alone, or pairs, or all three given together in normal diet. Lead showed no effect on weight gain or feeding, but increased U aminolevulinic acid (ALA) and raised uric acid. As reduces SGOT, with no change in uric acid. Pb + Cd reduce hemoglobin and hematocrit, and Cd reduces Pb effects on kidney, Cd also offsets some Pb driven gain in U-ALA. Cd + As reduce wt gain more than either alone, and drop Hb and Ht. Pb + Cd + As increases rbc, to higher levels than the sum of the separate metals. The presence of other metals reduces the Pb effects.

lead, arsenic, cadmium, combined stresses, toxicity, diet, nutrition, metabolic conversion, aminolevulinic acid, uric acid, nephrotoxicity, interactive responses
Interactions among Lead, Cadmium, and Arsenic in Relation to Porphyrin Excretion Patterns

In laboratory experiments, rats (168 M SD) were exposed to: LEAD Acetate at 200 ppm, CADMIUM Chloride at 50 ppm, and ARSENIC as Na Arsenate at 50 ppm; all added to usual diet for 10 wks. Measurements were made of urinary aminolevulinic acid (ALAO), uroporphyrin (UP) and coproporphyrin (CP); carbohydrate metabolism, and urea cycle. Pb alone caused increase in U-ALA and coproporphyrin, alters heme synthesis and pyruvate respiration; Cd alone had no effect on most processes, but inhibited oxidative phosphorylation, As alone increased U-coproporphyrin and uroporphyrin, inhibited pyruvic respiration. Cd + Pb and As + Pb have an additive effect on mitochondrial toxicity, biochemical systems and porphyrin excretion. As + Pb have additive effect on coproporphyrin but not on ALA or uroporphyrin. Pb + Cd + As will show either additive or antagonistic effect, depending on conditions selected.

lead, cadmium, arsenic, combined stresses, diet, metabolism, aminolevulinic acid, coproporphyrin, uroporphyrin, mitochondria, interactive responses
Occupational observations and clinical studies on workers in electrolytic production of chlorine are reported briefly. The workers (312 "exposed", 80% M, under 50 yr) were exposed to: CHLORINE, over 1 mg/m³ (their MPC); and MERCURY VAPOR, over their MPC (not given) for period from 1 to over 10 yr.

They were screened regularly. When compared with unexposed controls (278) there was an increased frequency of CNS and peripheral neural disorders, altered bioelectric activity of brain, myocardial dystrophy (chiefly Hg driven); systemic hypertension; chronic bronchitis and subatrophic rhinopharyngitis, chiefly Hg driven, gastritis, conjunctivitis, cholecystitis and altered liver function.
Factors Influencing Metabolism and Toxicity of Metals: A Consensus Report by the Task Group on Metal Interaction

Nordberg GF Ed

Factors Influencing Metabolism and Toxicity of Metals: A Consensus Report by the Task Group on Metal Interaction

This report reviews the work of a group organized by the Scientific Committee on Toxicity of Metals, part of the Permanent Commission and International Association on Environmental Health. A list of editorial committee members is provided. Topics include: Work and other Environment Factors (sources of metal toxicics, their transformations, affinities, sinks, physical-chemical interactions); Toxicology of Metals (independent or joint action in organism, sites, modes, synergies, examples of interactions; then systematic detail of toxicities and interactions among Arsenic, Selenium, Lead, Cadmium, Zinc, Iron, Calcium, Mercury; and discussion of other modulators: age, sex, nutritional status, smoking, other atmospheric pollutants, etc.

Toxic metals, sources of pollutants, metal-metal interactions, toxicology, arsenic, lead, cadmium, zinc, iron, calcium, mercury, selenium, environmental health, interactive responses
SOLVENTS

COMBINED STRESS EXTRACTS
**Biotransformation of Organic Solvents**

**Topics discussed include:**
Specific processes of oxidation (microsome CP450 catalyzed); hydroxylation, deamination, dealkylation; reduction; conjugation (e.g., ATP-driven glucuronic acid coupling), methylation, acetylation, etc.

**Roles of biotransformation, in making water-solubles, in metabolic activation (forming reactive intermediates, some more toxic than originals), induction of metabolizing enzymes. Examples of some specific xrefs among aromatics (benzene, styrene, toluene, xylene), halogenated hydrocarbons (chlorinated alkanes, ethylenes like TCE) other alkanes, alcohols, etc.**

**Metabolites as Tests for Exposure:** phenol for benzene, mandelic acid for styrene, hippuric acid for toluene. Interactions between solvents, drugs, ethanol.

**KEY WORDS**
solvents, combined stresses, biotransformations, oxidation, reduction, hydroxylation, conjugation, reactive intermediates, bioindicators of exposure, interactive mechanisms
In laboratory experiments human subjects and rats were pretreated with PHENOBARBITAL, then exposed to M-XYLENE (no data available). The enzyme inductions in both species in liver do not lead to enhanced metabolism of the absorbed M-X (eg at 400 mg/m\(^3\) inhaled) at lower levels; at these conc the normal biotransformations in liver are enough to metabolize total absorption pool. At higher conc of M-X (eg 2000-4000 mg/m\(^3\)) the normal mechanism is saturated, and PB potentiates the enhanced secretion of more M-methylbenzoic acid metabolite). It becomes fallacious to calculate absorbed doses of such organic solvents from excreted metabolites unless the exposures to PB and such drugs are also known.

**Extract**

<table>
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<tr>
<td>phenobarbital, xylene, combined stresses, solvents, toxicity, metabolism, liver enzyme induction, interactive responses</td>
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</table>
### Worker Exposures to Chemical Agents in the Manufacture of Rubber Tires: Solvent Vapor Studies

**Key Words:**
- solvents, combined stresses, rubber and tire industry, toxicity, toluene, benzene, alkanes, air sampling, interactive events.

**In occupational studies on rubber workers in 10 tire plants, exposure to solvents such as BENZENE, TOLUENE, various ALKANES were assessed by first examining job classes, processes, functions, and products; then classifying exposures as high, middle, or low (relative to TLV). Approx 5000 air samples were taken and assayed, and at a selected 200 points at the breathing zones of workers.**

**Mixed vapor conc in several samples exceeded the threshold limits (calculated by additive means) for mixed solvents. All of this was used as a basis for other studies of worker responses.**
The pharmacology of a wide variety of substances, and highlights on some of their interactions, are discussed. Acute events, such as formation of short-lived intermediates (TCE to asymmetric and symmetric epoxides, benzene to aryl epoxide, C₉S to epoxides and semioxide), and more long-lived intermediates (e.g., CH₂Cl₂ to CO₂, dichloromethane to CO₂, styrene to epoxide) are considered in terms of their role in toxicity. Other acute actions, on nerve cell membranes and energy metabolism (e.g., C₉S + TCE changes in mitochondrial energy production) are discussed. Certain chronic events in neural metabolism, protein synthesis, enzyme alterations, and some related neuropathies are considered. The clinical consequences and recovery from exposures, including the possibilities of certain reversals (e.g., early neurotoxicity due to n-hexane) are discussed.

**Key Words:**
- solvents, combined stresses, toxicity, industrial exposure, pharmacology, carbon disulfide, trichloroethylene, benzene, n-hexane, chlorinated hydrocarbons, reactive intermediates, interactive responses
Effect of Phenobarbitone and Starvation on Hepatotoxicity in Rats Exposed to Carbon Disulfide Vapor

Magos L, Butler WH

ENGLAND: MRC Toxicol Unit, Surrey


In laboratory studies rats (M albino) were exposed to: PHENOBARBITAL Sodium at 50, 50 mg/Kg IP, 24 hr before CARBON DISULFIDE at 2.0 mg/L inhaled (no other data) or 18 and 23 hr before DIETHYLDITHIOCARBAMATE at 500 mg/Kg injection. CS₂ induced liver histopathology; hydropic degeneration of centrilobular zone, only in rats pretreated with PB. Food deprivation for 24 hrs aggravated the CS₂ toxic effect, eg on Cytochrome P450.

phenobarbital, carbon disulfide, starvation, combined stresses, hepatotoxicity, solvents, serum enzymes, interactive responses
**Extract**

In laboratory experiments rats (M SD) were exposed to: ETHANOL at 5 g/Kg po 1x, then later: CARBON TETRACHLORIDE at 50, 100, 250, 1000, 10,000 ppm vapors; or TRICHLOROETHYLENE (data not avail) or PERCHLOROETHYLENE (no data) or METHYLCHLOROFORM (no data). EtOH pretreatment 18 hr before potentiates the toxicity & liver pathology for CCl₄ and TCE in short exposures (but not PCE). With EtOH and CCl₄ from 100-10,000 ppm for 2 hrs there is no change in serum enzymes SGOT & SGPT. EtOH 8 hrs before 25,50 ppm CCl₄ or 100 ppm TCE shows no potentiation, but does so when 2 hrs before 100 ppm CCl₄ or 4 hrs before 5000 ppm TCE.

**Key Words**

ethanol, solvents, combined stresses, toxicity, carbon tetrachloride, trichloroethylene, perchloroethylene, methylchloroform, serum enzymes, hepatotoxicity, interactive responses
In laboratory experiments human subjects (39 M adult 19-26 yr) were exposed to: TRICHLOROETHYLENE at 200 ppm inhaled for 2 hr; and ETHANOL at 0.35 g/Kg po. Tests of behavioral performance included pursuit rotor task, binary light choices; physiological indices included heart rate and any arrhythmia. TCE + alcohol impaired mental capacity, information handling, more than each stressor alone below its MAC. Heart rate is higher than with TCE or EtOH alone. More sinus arrhythmias are produced by the pair than by each alone. TCE metabolism is inhibited by alcohol, an event which can be dangerous in the work environment.
**REPORT DOCUMENTATION PAGE**

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In laboratory experiments human subjects (7, healthy, 19-46 yr) were exposed to: TRICHLOROETHYLENE at 20, 100, 200 ppm vapors and skin exposure for 1, 3, or 7.5 hr; and ETHANOL, as beer (1 qt. Schlitz in 30 min). At 71 hr after TCE dose, subjects were rechallenged with EtOH (as 9 cc 100 proof vodka in orange juice), (others were rechallenged at 2.5 and 5.5 hr). The special response as skin lesions, with vasodilation of skin vessels, as a transient event (flush). Repeated TCE exposures are needed before the alcohol challenge could initiate the dermal response. This TCE flush reaches max intensity 30 min after onset, then fades in 60 min, on face, neck, shoulders, back.

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trichloroethylene, ethanol, combined stresses, dermal response, toxicity, solvents, degreasers flush, interactive responses

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In laboratory experiments rats (F, SD) were exposed to COLD at 2-4°C or HEAT at 31-33°C; or ETHANOL 50% v/v water at 4 g/Kg by intubation. One of these three stresses was given 18 hrs before CARBON TETRACHLORIDE was given at 0.25 cc/Kg. Liver triglyceride accumulation and SGPT were measured. EtOH or cold exposure potentiated SGPT response to CCl₄, but did not potentiate liver triglyceride accumulation response to CCl₄. Thyroidectomy did not prevent the EtOH-CCl₄ interaction. EtOH treated rats at 32°C had a reduced response to CCl₄.

**KEY WORDS**
ethanol, carbon tetrachloride, combined stresses, heat, cold, solvents, toxicity, liver triglycerides, interactive responses
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| Arch Environ Hyg 1967;14:447-449        |

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In laboratory experiments rats (M SD) were exposed to: single ALIPHATIC ALCOHOLS, ethanol, methanol, n-propanol, butanol, in single doses at approx 40% of LD50, by intubation. At 2 or 16-18 hr later, CARBON TETRACHLORIDE at 1,000 ppm was given by inhalation for 2-2½ hrs. SGOT levels 24 hrs later were raised 3-200x controls with the alcohols alone. CC14 alone caused no rise in SGOT. Ethanol dose 16-18 hr prior to CC14 potentiated CC14 liver toxicity; this was not unique to the ethanol. Sec- and tert-butyl alcohols were more effective than n- or i- butyl alcohols. No potentiation was seen if alcohol was given 2 hrs before exposure. The event needs some metabolic processing. In industrial practice since alcohol doses under 1 g/Kg are not potentiating, this event is not likely to occur in an 8 hr day.

| 19. KEY WORDS                         |

| carbon tetrachloride, alcohols, combined stresses, toxicity, ethanol, methanol, n-propanol, butanols, SGOT, solvents, interactive responses |

| 20. NOTES                              |
In laboratory experiments rats (41) were exposed to: CARBON MONOXIDE at 958 ppm for 90 min in chamber; or HYPOXIA, altitude (data not avail); then were given CARBON TETRACHLORIDE at 3799 ppm or 5140 ppm for 30 min. 24 hrs later, blood was studied for SGOT, SGPT. SGOT and SGPT rise 3x levels of CCl₄ alone. In hypoxic atmosphere, instead of CO, then CCl₄, there was no change in enzymes due to combined events. The effect of CO on CCl₄ hepatotoxicity does not appear to be due to induced tissue hypoxia. But this pair, CO and CCl₄ can become an interactive industrial hazard.
In occupational observations and clinical studies of workers in 5 industrial groups, car painters (100, av age 35.5 yr) were exposed to mix of organic solvents including toluene and xylene at levels about 1/3 of Finnish TLV for av 14.8 yr; rayon viscose workers (206, av age 49.3 yr) were exposed chiefly to carbon disulfide, many times over 20 ppm, for av 15 yrs; printers (26, av age 39.5 yr) were exposed to toluene at 60-200 ppm (est) for av 19.7 yr; laminators (98, av 29.5 yr) were exposed to styrene at 7-4,700 mg/L for 5 yr; other workers with solvent mixes (56, av 38.8 yr) were exposed to low and high levels for av 9 yrs.

Most severe damage was from possible synergistic exposures to aromatic and halogenated HC mixes (behavioral). There were changes in all groups, in sensory, cognitive, and motor functions, with special effects, eg styrene on visuomotor acuity, C2S changes in verbal ability and finger-hand dexterity.

**Key Words**
solvents, combined stresses, viscose industry, car painting, printing, styrene, carbon disulfide, toluene, behavioral change, cognitive function, sensory loss, psychomotor change, interactive responses

**Notes**
Several different studies on these workers are reported in this journal, from 1976-1981
Behavioral Effects of Long-Term Exposure to a Mixture of Organic Solvents

In occupational observations car painters (102) from 6 garages were exposed in their work to mixtures of solvents approximately av 1/3 TLV for Finland, and including: TOLUENE 30 ppm, XYLENE 528 ppm, BUTANOL 68 ppm, etc. These workers were compared with a referent group of locomotive workers (102) without these solvent exposures. There was seen a general impairment in behavior, performance, and personality. Most affected were: visual intelligence (Wechsler), verbal memory (digit span), some psychomotor performance (tapping, reaction times, bar press), and reduced emotional reactivity.

solvents, combined stresses, car painters, toluene, xylene, butanol, toxicity, behavior, personality, intelligence, memory, psychomotor performance, reaction time, interactive responses

Several different studies on these workers were reported in this journal from 1976 on.
In occupational and clinical studies, car painters (102) from several garages were studied for responses to exposure to a mixture of solvents, and compared with a non-exposed referent of locomotive engineers (102). The solvent mixture included: TOLUENE, XYLENE, BUTYL ALCOHOL, METHYL-ISOBUTYL-KETONE, ACETONE, ETHANOL, ISOPROPANOL, local "WHITE SPIRITS". Exposure levels averaged 1/3 Finland TLV, with range of 4-212% of this value. Various neurological findings included: poly-neuropathies, reduction in nerve conduction velocities in peripheral and spinal cord motor neurones, changes in EEG (but many changes in EEG were also seen in the locomotive engineers), and signs of diffuse brain damage in 32 painters.

### Keywords
- solvents, combined stresses, shop painters, neuropathology, toxicity, paints, toluene, xylene, ketones, alcohols, interactive responses

### Notes
Several different studies on these workers were reported in this journal, from 1976 on.
REPORT DOCUMENTATION PAGE

1. REPORT NUMBER
2. GOVT ACCESSION NO.
3. CATALOG NUMBER
   A0150

4. TITLE (and Subtitle)
   Symptoms of Car Painters with Long Term Exposure to a Mixture of Organic Solvents

5. REPORT DATE
   1980

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)
   Husman K

8. CONTRACT OR GRANT NUMBER(S)
   G; Jahnsson Fdn

9. PERFORMING ORGANIZATION NAME AND ADDRESS
   FINLAND: Kuopio Regnl Instit Hlth

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS

11. CONTROLLING OFFICE NAME AND ADDRESS

12. REPORT DATE
   1980

13. NUMBER OF PAGES AND REFS
   14P 27P

14. PUBLICATION
   Scand J Work Environ Health
   1980 (1);6:19-32

15. DISTRIBUTION STATEMENT

16. EXTRACT
   In occupational observations car painters (M 102) in repair garages were compared with a referent group of locomotive engineers (without solvent exposures). The painters were exposed to a mixture of SOLVENTS including toluene, xylene, butyl acetate, methyl-isobutyl ketone, isopropanol, ethyl acetate, acetone, ethanol, and the local "white spirit". The exposure level was estimated av 1/3 Finland TLV, but ranged from 4-212% of this. There were findings of change in memory, vigilance, prenarcotic syndromes, fatigue, and various neurological symptoms; as well as irritated skin and mucous membranes. Their data assembly considered the pre-existing diseases (eg tuberculosis, diabetes) present in 4 cases, also usage of cigarettes, alcohol, and medications. The acute symptoms eg of nausea and vomiting were found most during the work day. Effects were calculated as if the component solvents were additive, with potentiation uncertain.

17. KEY WORDS
   solvents, combined stresses, shop painters, neuropathology, toxicity, paints, toluene, xylene, ketones, alcohols, interactive responses.

18. NOTES
   Several different studies on these workers were reported in this journal, from 1976 on.
In occupational observations, car painters (102) exposed in their work to TOluene, XylenE, Butanol, Trichloroethylene, MethylButyl-Ketone, various thinners each at levels estimated at 1/3 TLV. This group was compared with locomotive engineers (102) not exposed to this group of stresses. There were found CNS changes including abnormal vibration sensitivity, with 43% painters having increased thresholds at about 100 Hz, also decreases to light touch and pain sense. There was also ataxia, tremor, rapidly alternating movements of the finger; also dizziness, fatigue; difficulties in concentration, impaired memory, and reduced speed of response.

Key words: solvents, combined stresses, car painters, trichloroethylene, butanol, methylethyl ketone, vibration sense, ataxia, toluene, xylene, interactive responses, neuropathology

Notes: Several different studies on these workers are reported in this journal.
In occupational observations and clinical studies, workers (200+) were exposed to these and other solvents: STYRENE (data not avail) CARBON DISULFIDE est range 10-30 ppm; m-XYLENE est range 100-200 ppm. Beyond the narcotic effects shown by most organic solvents, abnormal EEGs were usual among most exposed to solvents (excess slow theta waves at 4-7 Hz, sometimes localized). There was a slowing in nerve conduction velocity, changes in EMG, and various complaints indicating CNS or peripheral neural change. EEG changes are also caused by styrene (along with changes in mandelic acid), by m-xylene (occipital EEG changes), and C2S.

**KEY WORDS**

solvents, combined stresses, carbon disulfide, xylene, plastics workers, neuropathy, EEG, nerve conduction velocity, theta waves, interactive responses
Interactive responses to several chemicals by workers in three different trades are reported in case form. A shoemaker (52 yr) exposed to trichloroethylene, thinners, tetrahydrofurane for several yrs also regularly ingested Paraflex compound (which included acetylsalicylic acid, and dextrapropoxyphene). Liver biopsy showed fatty changes, siderosis, enlargement, and persistent increase in ALAT. A painter (52 yr) exposed to various solvents and thinners, received digoxin, verpamil (isoptin), paracetamol (Lunedon). He had at various time been an inpatient for cholecystitis, slipped disc, and cardiac infarction. Liver biopsy showed fatty changes, and he had increased ALAT and ASAT. Another painter (42 yrs) exposed to solvents, taking digoxin, hydralazine, propanolol, and with a history of hypertension and cardiac enlargement, showed liver fatty changes, also raised ALAT and ASAT.

**KEY WORDS**

solvents, drugs, combined stresses, acetylsalicylic acid, dextrapropoxyphene, shoemaking, industrial painting, toxicity, liver pathology, metabolism, interactive responses.
In laboratory studies with rats (F Wistar adult), they were exposed to: ETHANOL at 2 g/Kg IP, then CARBON DISULFIDE at 20, 400 ppm inhaled 8 hr. This exposure did not change blood alcohol elimination rate. EtOH fall is associated with acetaldehyde (AcEt) rise plateau. After the same EtOH CS₂ exposure was repeated at 400 ppm for 8 hr, in 3, 6, 12 exposures at 2 day intervals. There was no change in EtOH elimination. When DIMETHYLDITHIOCARBAMATE at 50 mg/kg or DIET-DITHIOCARBAMATE at 50 mg/Kg were given IP, 20 min later AcEt levels went up 3X. TETRAMETHYLTITURAM DISULFIDE at 0.06-1.0 g/Kg given orally raised AcEt, with EtOH elimination slightly retarded only after 0.25 and 1.0 g/Kg. DISULFIRAM at 1g/Kg oral 16 hr before EtOH load raised AcEt to 5X without effect on EtOH elimination.

**KEY WORDS**
carbon disulfide, thiurams, ethanol, acetaldehyde, toxicity, metabolism, dimethyldithiocarbamate, diethyldithiocarbamate, tetramethylthiuram disulfide, disulfiram, interactive responses
**Influence of Inhaled Carbon Disulfide on Acetaldehyde Production and Liver Function in Alcoholized Mice**

Freundt KJ, Lieberwirth H

**STANDE**

**11. CONTROLLING OFFICE NAME AND ADDRESS**

W GERMANY (FR): Univ Wurzburg Instit Toxicol-Pharmacol

**12. REPORT DATE**

1974

**13. NUMBER OF PAGES AND REPS**

1P no R

**14. PUBLICATION**

Naunyn Schmiedbergs Arch Pharmacol 1974 (Suppl);282:R21 (abstract)

**16. EXTRACT**

In laboratory experiments human subjects (adult) were exposed to: CARBON DISULFIDE at 20 ppm for 8 hr; also ETHANOL at levels to maintain blood at 0.7% EtOH. This level did not change with CS₂ up to 40 or 80 ppm. Blood acetaldehyde was 2X normal at 24 hr after end of 8 hr exposure to CS₂ at 22 ppm. CS₂ at 20 ppm for 8 hr/day x 5 days raises blood acetaldehyde about equal to one exposure to CS₂ at 80 ppm in 8 hr. There is no evidence of an "antabuse" syndrome (inhibited aldehyde dehydrogenase). After one or more CS₂ doses, total serum bilirubin rose to 2X normal in alcoholized subjects; total protein and uric acid were at the upper limits of normal.

**19. KEY WORDS**

carbon disulfide, ethanol, combined stresses, antabuse syndrome, aldehyde dehydrogenase, acetaldehyde, interactive responses
**EXTRACT**

In laboratory studies, separately with rats and humans: rats (F, Wistar) were exposed to: CARBON DISULFIDE at 20 ppm in air 8 hr; also ETHANOL 2 g/Kg IP for 4 hr. Human subjects (12 M 20-32 yr) were exposed to: CS₂ at 20, 40, 80 ppm in air for 8 hr; with EtOH at start at 0.57 cc/Kg in orange juice 1 x than 0.047 cc/Kg every 15 min, then for 16-24 hr, after 8 hr of CS₂. (These inhalations were to simulate 1 work week). Rats and man were similar in sensitivity to CS₂ after EtOH. CS₂ induces inhibition of aldehyde dehydrogenase in blood. When EtOH is taken blood acetaldehyde rises. EtOH use at 16-24 hr after 8 hr of CS₂ causes an extra rise of blood acetaldehyde. There are no interactions between EtOH at 0.8% and CS₂ 10 ppm (like antabuse effect). In rats loaded with EtOH, blood acetaldehyde rises after 1 short 20 ppm CS₂ dose.

**KEY WORDS**

carbon disulfide, ethanol, combined stresses, acetaldehyde, toxicity, aldehyde dehydrogenase, interactive responses
In laboratory experiments rats (50+ SD) and monkeys were exposed to: ETHANOL, METHANOL, ISOPROPANOL, TOLUENE, by inhalation, each in range to 11,000 ppm; then METHYLENE CHLORIDE at 50, 500, 5000 ppm vapors or IP in 1 hr exposure. In rats (sacrificed 2, 4, 6, 8 hr post exposure) MeCl 50-5000 ppm forms COHb in a linear dose-response. MeCl at 5000 ppm for 1 hr + Ethanol inhibits formation of COHb at 1350 and 8000 ppm, but does not alter levels at 11,000 ppm. Methanol given IP 30 min before MeCl at 5000 ppm inhibits COHb. In monkeys, all solvents tested produce inhibition of MeCl-induced COHb. MeCl to 1000 ppm 3 hr + MeOH 330 ppm causes peak COHb levels. MeCl 4800 ppm + MeOH 4300 ppm + T 1800 ppm inhibits COHb as in rat. MeCl 4800 ppm alone 4 hr causes peak COHb. There is no MeOH potentiation of MeCl COHb in rat or monkey, but there is in man. Rat and monkey MeOH potentiation of COHb is not a good model for man.
**Extract**

In laboratory experiments on human subjects (39M, 17F, 18-32 yr), METHYL CHLORIDE at 100, 200 ppm (route unknown) was given for 3 hr; and DIAZEPAM at 10 mg oral was given, in treatments with each or both. Diazepam reduces by 10% scores on behavioral performance (visual vigilance, time discrimination, eye-hand coordination, mental alertness). MeCl at 200 ppm alone has only a marginal effect on performance. But D + MeCl show impairment which is additive.

**Key Words**

methyl chloride, diazepam, combined stresses, toxicity, behavioral effects, interactive responses
In laboratory experiments rats were exposed to: PHENOBARBITAL 50 mg/Kg IP in pretreatment 1-2 days before reposure to one of the following: CARBON TETRACHLORIDE at 0.01-0.06 cc/Kg; or CHLOROFORM at 0.1, 0.3, 0.5 cc/Kg; or METHYLENE CHLORIDE at 0.2-1.0 cc/Kg; or METHYL CHLOROFORM at 0.3-2.0 cc/Kg; or TRICHLOROETHYLENE at 0.3-2.0 cc/Kg; or PERCHLOROETHYLENE at 0.3-2.0 cc/Kg. The PB is a liver microsome enzyme inducer. CCl4 toxicity is associated with metabolism eg to CO2 and free radicals. High doses inhibit liver metabolizing enzyme systems. PB potentiated toxicity of CCl4 (doses as low as 0.025-0.05 cc/Kg); the latter dose + PB changes SGOT, causes centrilobular fatty infiltration of liver. PB also potentiates toxicity of CH2Cl2. PB + CHCl3 raises SGOT 100 X CHCl3 alone.

phenobarbital, solvents, combined stresses, carbon tetrachloride, chloroform, methylene chloride, methyl chloroform, trichloroethylene, perchloroethylene, SGOT, toxicity, interactive responses.
In laboratory experiments rats (600 M) were exposed to: PERCHLOROETHYLENE, at 3.9 g/Kg po, alone, or with either: BENZENE at 3 g/Kg po or TOLUENE (dose not avail). The treatments included several combinations and several dose levels of each. In the assessment of LD50 and tests of additive joint toxicities, a rigorous statistical probit design was used. PCE enhances the toxicity of B, in a slightly less than additive way. PCE also augments T toxicity (with other effects on nervous system). The departures in additivity have unknown mechanisms, not predictable, nor describable in usual terms of synergy or potentiation.

**Key Words**
- perchloroethylene, benzene, toluene, combined stresses,
- toxicity, solvents, neuropathology, interactive responses
In laboratory experiments human subjects (6 M, 21-45 yr) were exposed to: TRICHLOROETHYLENE at 300, 1000 ppm by inhalation, prior to dose of: ANAHIST (THONZYLAMINE HCl) at 50 mg oral, alone or after TCE, and 30 min before performance tests below; or MEPROBAMATE (EQUANIL) given at 800 mg orally, alone or + TCE, immediately before performance test; or ETHANOL at 35 cc/70 Kg orally over 20 min. Performance tests included steadiness, flicker fusion, depth perception, and various illusions. Anahist alone had no effects. Equanil alone impairs other performances: learning, driving skills (but showed no special effects in the lab). TCE did not augment these CNS depressant effects. TCE effects themselves were not enhanced by Anahist or Equanil, on flicker fusion, pegboard testing, but TCE in chronic doses yields intolerance to ethanol. TCE causes potentiation in CNS drugs, and can be a factor in the workplace since 1/3-1/2 adults use these drugs.
### Extract

In laboratory experiments rats (F) were exposed to: PHENOBARBITAL, at 37.5 mg/Kg IP for 4 days in preconditioning to stimulate max enzyme activities in the liver; then TOLUENE at 430 mg/Kg IP; or TRICHLOROETHYLENE at 730 mg/Kg; or a mix of these two (T + TCE). TCE + T cause suppressed excretion of hippuric acid (a main metabolite of T) but reduce the amount of urinary trichloro-compounds (from TCE). TCE is a non-competitive inhibitor of side chain hydroxylation of T, and the reverse is also true. In other studies, T in rats suppresses biotransformation of benzene to phenol, also styrene to hippuric acid. There is also discussion of kinetics of absorption and excretion in the lung, and of processes in microsomal oxidation.

### Keywords

- phenobarbital, toluene, trichloroethylene, combined stresses, toxicity, enzyme induction, hippuric acid, metabolic inhibition, interactive responses
In laboratory experiments rats (F Wistar) were exposed to: PHENOBARBITAL at 75 mg/Kg IP 1x/day for 4 days, pretreatment; then TOLUENE at 0.43 g/Kg IP; or BENZENE at 0.44 g/Kg IP. PB shortened the narcotic action of T, reduced the leukopenic action of B, and generally enhances drug metabolism and thus reduces toxicity. PB, via hepatic microsomes, raises T side chain hydroxylation, towards benzyl alcohol; and raises B aromatic hydroxylation to phenol. PB can thus be used in therapy of solvent intoxication by its induction of drug metabolizing enzymes.

**Key Words**
- phenobarbital, toluene, benzene, combined stresses, liver enzymes, metabolism, toxicity, interactive responses
**In laboratory experiments rats (M albino) were exposed to:**
1,2-DICHLOROPROPANE (DCP); 1,2,3-TRICHLOROPROPANE (TCP); or PERCHLOROETHYLENE (PCE). No doses were available, but each is given in 6 concentrations in various combinations, by inhalation through 7-86 days. Measurements were made of body wt, catalase and cholinesterase activity, RBC and WBC counts, and of neural activity. Combined effect calculations from exposures were made using Finney's formula, and effects were found to be additive.

**Keywords:**
dichloropropane, trichloropropane, perchloroethylene, combined stresses, Finney's equation, cholinesterase, catalase, toxicity, hematology, solvents, interactive responses
In laboratory experiments rats (albino) were exposed to: METHANOL (no data given); also 2,6-DIMETHYLPHENOL (no data). Three treatments were: 70% M + 30% DMP, 50% M + 50% DMP, 30% M + 70% DMP, all treatments intragastric in 4 doses. The measured and calculated LD$_{50}$s were determined for the mixtures. Most mixtures show a reduced LD$_{50}$ or XPL compared with the individual or summed doses for the components (potentiation). "Potentiation Coefficients" for the mixes were: 2.70 for 70M/30DMP, 2.38 for 50M/50DMP, and 1.94 for 30M/70DMP. In other studies with chronic inhalation exposure with endpoint the duration of swimming, the same potentiations were seen. No other data were available. Multifactorial and multiregression analyses were discussed.

**Key Words**

methanol, 2,6-dimethylphenol, combined stresses, toxicity, interactive responses
In laboratory experiments, human subjects (12 M, healthy, 19-35 yr) were exposed to XYLENE (an industrial mixture including: ethylbenzene 40.4%, p-xylene 1.4%, m-xylene 49.4%, o-xylene 8.8%). One group received X at 870 mg/m³ (200 ppm) continuous exposure, while at rest for 30 min, then physical EXERCISE at 50, 100, 150 Watts for 90 min (X exposure also). A second group received 435 mg/m³ (100 ppm) while at rest 30 min, then during 90 min of exercise. In both dose groups, about 60% X was taken up in the lungs, and with increasing work (and ventilation) more X was taken up. Analyses showed tissues in which solubilities were higher took up these solvents, in relation to their dose fraction and differences in solubility. Beyond this, there were no combined effects.

**Key Words**: industrial xylene, combined stresses, ethylbenzene, m-xylene, o-xylene, p-xylene, exercise, ventilation, solubility, interactive responses

**Notes**: For Part II (Adipose tiss) see Engstrom 1978
For Pt III (Neural tiss) see Gamberale 1978
Petroleum Hydrocarbon Toxicity Studies. Animal and Human Responses to Vapors of Mixed Xylenes

Cats (4 mixed breed) were given MX at 41/L (route not avail) and all died in 2 hrs, after salivation, ataxia, spasm, and other CNS changes. Rats given 43 mg/L (6000 ppm) had 100% mortality, starting at 2.5 hr; with dose of 580 ppm they had no mortality in 2.5 hr. Beagles given MX at 0.77, 2.0, 3.5 mg/L 6 hr/day for 5 d/wk for 13 wk showed no real effects. The effects of these mixtures are further discussed.

mixed xylenes, combined stresses, solvents, toxicity, neuropathology, interactive responses

ERK 1979 to Tox Hazards Res Unit, WPAFB
JMK 1979 to NY State Vet Coll, Cornell Univ Ithaca NY
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<td>In laboratory studies human subjects (8M, 24-30 yr) were exposed to: DIAZEPAM (D), 10 mg/70 Kg oral as 2 mg tabs; also ETHANOL (E) 0.78 cc 96% Et/kg, diluted to 30% v/v. These were given in various sequences, with several psychomotor and cognitive tests taking 1-3 hrs for series of 10 min tests. Each alone (D),(E) reduced concentration, attention; E+D augmented these subjective impressions. E reduced a hand tracing score, increased various error rates. D markedly impaired psychomotor functions, and reduced flicker fusion score. E + D further reduced scores of simple psychomotor and complex coordination tests. D itself impairs these performances, and enhances synergistically effect of E.</td>
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<td>diazepam, ethanol, combined stresses, psychomotor functions, cognitive performance, interactive responses</td>
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| 20. NOTES | |
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**DD Form 1 JAN 73 1473 (NCR)**
Interaction of Chloral Hydrate and Ethanol in Man. Metabolism

Sellers EM, Lang M, Koch-Weser J, LeBlanc E, Kalant H

Harvard Med Schl, Depts Med & Pharmacol at Mass Gen Hosp, Boston, MA


In laboratory studies human subjects (5M, fit, 21-29 yr) were exposed to: ETHANOL at 0.5 gm/Kg diluted with orange juice; also CHLORAL HYDRATE at 15 mg/Kg. Treatment conditions were: E; E 1 hr after C; C; C for 7 days, last C dose 12 hr before E. E, if given 30 min after C (relative to C alone caused higher and longer conc of plasma trichlorethanol and urine TCethanol glucuronide. C affects E metabolism, and causes peak plasma E conc to be reached earlier and stay higher than E alone. The higher blood E is due to competitive inhibition of alcohol dehydrogenase by TCet. E stimulates NADH production, so increases rate of chloral hydrate reduction to TCet by liver alcohol dehydrogenase. The metabolism of both is interactive, altered by combined administration.

KEY WORDS

ethanol, chloral hydrate, combined stresses, NADH metabolism, detoxication, interactive responses
In laboratory studies human subjects (M, ages 20-30 yrs) were exposed to: ETHANOL, 20 gm, as 80 or 120 cc on an empty stomach); also CARBON MONOXIDE at 175 ppm for 1,90,180 min; or TRICHLOROETHYLENE at 10,75,300 ppm for 135-150 min. These are given individually, and their effects compared. Ethanol as a reference substance at levels over 0.3 g/L caused marked decrease in performance on a variety of psychomotor functions. CO and TCE here had no effect on performance. The potential effects on performance of these substances (each separately at doses in occupational or "social range) in combined effects exceeding tolerance, have not been studied here.
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<td>Synergism, with Special Reference to Central Nervous System Depressants</td>
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<td>Phila Coll Pharmacy &amp; Sci, Dept Pharmacol, Phila PA</td>
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<td>1963</td>
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<td>J Pharmaceut Sci 1963 (9);52:819-832</td>
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<td>16. EXTRACT</td>
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<td>Concepts of interaction, synergy, potentiation in the pharmacological context are discussed in detail. Examples of these interactions, among analgesics, narcotics and narcotic antagonists, anesthetics, hypnotics are considered.</td>
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<td>therapeutic drugs, multiple drug administration, work-drug interactions, analgesics, antagonists, anesthetics, hypnotics, biotransformation, synergy, potentiation, interactive responses</td>
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Several problems of worker illnesses and injuries for which over-the-counter and non-prescription therapeutic remedies are sought were discussed. Interactions between prescription drugs taken by many, the related illnesses or conditions, the OTC medications, and work performance are considered. Modes of interaction are discussed, and examples provided among remedies sought for dermatitis, pulmonary disorders, rhinitis, head injuries & musculoskeletal aches, infectious disease, GI discomforts, and the like. Many examples are given of clear problems caused by the indiscriminate use of self-medication and the possible extension of hazard on the job.

**Key Words:**
therapeutic drugs, self-medication, work-medication interactions, combined stresses, dermatitis, neomycin, peptic ulcer, cimetidine, alcohol, coffee, diazepam, tetracycline, photosensitivity, depression, pulmonary disorders, antihistaminics, chlorpheniramine
workplace combined stresses, interactive responses
This deals with those drugs taken by workers as legitimately prescribed for treatment of illness by private physicians or health maintenance services. There are discussed several classes of drugs commonly taken, their primary and side effects, their impact on function in the working environment, on psychomotor performance, on energy, on physiological processes; and the combined effects of these prescription drugs, the illnesses for which they are intended, OTC drugs which may be taken concurrently, and various hazards and stresses on the job which may then become real dangers. Classes of substances discussed are: hypnotic drugs, antianxiety drugs, antipsychotics, and anticonvulsants.
This is the second of a series dealing with prescription drugs used by workers for treatment of ongoing disease. Several antibacterial classes are discussed. These include the penicillins, cephalosporins, erythromycin, the tetracyclines, and chloramphenicol. Several concepts are developed, around the joint impact on the worker and workplace concerning the illness being treated, the primary and side effects of these drugs, OTC drugs selected and taken concurrently for other minor illness, and these drug effects, the combined drug interactions, and possible synergistic effects of these factors and toxic or other stresses in the workplace.

**KEY WORDS**

work-medications interactions, penicillin, cephalosporins, erythromycin, clindamycin, lancomycin, tetracyclines, chloramphenical, antimicrobial drugs, workplace combined stresses, interactive responses

**NOTES**

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<td>Potential Effects of Medications at Work. 3. Antimicrobial Drugs (Cont’d)</td>
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<td>Occup Hlth Safety 1981 (6);50:26-30,50</td>
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<td>This is the third of a series dealing with prescription drugs used by workers for treatment of ongoing disease, and interacting with their performance in the work environment. The group here includes: aminoglycoside antibiotics (and such factors as ototoxicity), the sulfonamides, antitubercular drugs such as isoniazide, ethambutol, rifampin, and antifungal preparations. The interactions possible converging on workplace safety and performance of these drugs, the illness for which they were given, OTC drugs possibly taken concurrently for minor ailments, their prime and side effects, hazards such as chemical toxics in the workplace and synergies and potentiations, are all considered.</td>
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<td>work-medication interactions, aminoglycoside antibiotics, streptomycin, neomycin, kanamycin, ototoxicity, nephrotoxicity, sulfonamides, isoniazid, ethambutol, rifampin, amphotericin B, methenamine, antimicrobial drugs, workplace combined stresses, interactive responses</td>
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<td>Please refer to other parts of this survey: 1. Pharmacology, OHS 1981 (2);50:48-49,52 and 2. Antimicrobial Drugs, OHS 1981 (4);50:33,35</td>
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Some alterations in drug metabolism by such environmental chemicals as Lead, Insecticides, PCBs and PBBs, and their modes of action are discussed. Changes induced in therapeutic drug transformations by components of cigarette smoke and other sources eg of polycyclic hydrocarbons, also their relationships to altered drug bioavailability are considered. Other effects on systems of mixed function oxidases are discussed. Other interactions of nutritional components and drugs and their availability are considered.
**Pharmacological Implications of Microsomal Enzyme Induction**

A variety of topics are discussed: the characteristics of enzyme inducers; effects of enzyme induction on drug action; tests for enzyme induction, mechanisms of microsomal enzyme induction by polycyclic hydrocarbons and drugs; effect of drugs on electron transport systems in liver microsomes; enzyme induction variations in different species; hormone regulation of drug metabolism, special problems of chemical roxics, insecticides carcinogens, etc.

**Key Words**
- enzyme induction, liver microsomes, toxics metabolism, environmental hazards, barbiturates, interactive responses
**Effect of Disease States on Plasma Protein Binding of Drugs**

**Author(s)**
Reidenberg M

**Publication**
Med Clinics North Amer 1974 (5);58:1103-1109

**Extract**
This discusses the problems of achieving therapeutic concentration of desired drugs in the face of altered pharmacokinetics associated with various illnesses. In poor renal function with abnormal excretion, altered metabolic paths and physical chemistry, there are constraints particularly on binding with organic acids and bases. Hypoproteinemia modifies binding, raising the unbound fraction and increasing available drug and effect. Other events concerned with liver cirrhosis, and concurrent drug therapy, are considered.

**Keywords**
drugs, protein binding, therapeutics, renal function, cirrhosis, drug-disease interactions, combined environmental stresses, chemical-drug interactions
**Primary discussion** is about pharmacokinetic interactions. Events which reduce amounts of drugs at site of action are discussed. These include reduced absorption, inhibition of transport to site of action, increased activity of drug metabolizing enzymes, and enhanced drug excretion. Activities which result in more drug agent delivered to action site include: altered protein binding, inhibitions of metabolism, and reduced kidney excretion. Among non-pharmacokinetic events discussed are interactions at common receptor sites on various cells, and especially on sensory receptors and neuromuscular junctions.
DRUGS

COMBINED STRESS EXTRACTS
In laboratory experiments, human subjects (10 M fit av age 22.8 yr) received ETHANOL 0.4-0.8 g/Kg, then were exposed to M-XYLENE at 636 mg/m³ or 1,218 mg/m³, in 4 hr inhalation. Since some solvents act via the vestibular apparatus, psychophysiological tests included disturbances in equilibrium (body sway etc), gaze deviation nystagmus, also extraocular muscle balance, critical flicker fusion. Xylene at the higher dose antagonized the ethanol effect on vestibular function. These combined effects do not follow the kinetics of the individual agents, so may sometime be additive or antagonistic.
**The Rate of Aniline Metabolism in Vivo in Rats Exposed to Aniline and Drugs**

**Wisniewska-Knypl JM, Jablonska JK**

**Xenobiotica 1975;5:511**

In laboratory studies rate (albino Wistar) were exposed to a complex array of drugs; with design including pre-treatment with PHENOBARBITAL SODIUM (microsomal enzyme inducer) at 80 mg/kg/day for 4 days IP; or CYCLOBARBITAL at 150 mg/kd/day x 4 days orally; or PHENACETIN at 1 g/kg/day x 6 or 14 days oral; or SKF-525-A (a microsomal enzyme inhibitor) stopped 30 min before "study" and given IP at 50 mg/kg; or 3,4-BENZPYRENE (microsomal enzyme inducer) given IP 45 mg/kg 72 hr before study. (Phenobarb, Cyclobarb, Phenac were stopped 24 hrs before the study). ANILINE was given, at 150 mg/kg/d x 3d or 6d sq; or 50 mg/kg/d x 30d. Aniline metabolism in vivo stimulated by Phenobarb, benzpyr, inhib by SKF525A. Aniline metab vivo/vitro stim by cyclobarb & phenac; pretreat with An, impaired An, met, in vivo. Other mixes stimulated Aniline metabolism.

**aniline, drugs, combined stresses, phenobarbital, cyclobarbital, phenacetin, benzpyrene, SKF-525A, metabolism, liver enzymes, interactive responses**
In laboratory studies human subjects (16 students, ages 21-29 yrs) were exposed to: CLEMIZOL (Allercur, antihistaminic and tranquilizer) at 40 mg; DIPHENHYDRAMINE (Benadryl, antihistaminic and sedative) at 50 mg; or TRIPLENNAMINE (Pyrabenzamine, antihistaminic and sedative) at 50 mg. One of these three was selected in a particular pretreatment, in 4 capsule, one taken at noon and one at evening meal on day prior to test, then one at breakfast on test day and one 1 hr nefore test. At that time, ETHANOL was given, alone or with pre-treatment drug at eg 45 cc/68 Kg, 3 oz 100 proof bourbon, mixed, drunk in 30 min. Tests included: delayed auditory feedback, special reading, counting, speech, pursuit tracking. Ethanol impaired mental and motor performance, as expected. Antihistaminics alone did not impair mental performance. Effect of E was not impaired by C, but E potentiated D effects on pursuit test.
MISC/CHEMICAL

COMBINED STRESS EXTRACTS
In lab studies with rats (350 pairs), the following substances were administered in pairs in various combinations, mixed 1:1 v/v and LD₅₀ oral dose ascertained and compared with individual LD₅₀. These included: acetone, acetonitrile, acetophenone, acrylonitrile, aniline, butyl cellosolve, butyl ether, carbon tetrachloride, diethanolamine, dioxane, ethanol, ethyl acetate, ethyl acrylate, ethylene glycol, formalin, isophorone, morpholine, nitrobenzene, phenyl cellosolve, polyethylene glycol, propylene oxide, tergitol nonionic XD, toluene, trichloroethylene, and Ucon fluid. The data were inserted into Finney's model equation to determine whether the effects were additive. Nine pairs showed ratios of predicted to observed values of 0.23-0.4 (below additive) and nine were as high as 2.7-5.09 (supraadditive). The additivity condition requires that the regression lines for separate chemicals acting jointly be parallel and similar modes of action.

**Key Words**

industrial chemicals, combined stresses, toxicity, lethality, additive models, interactive responses
## Extract

In laboratory studies rats (M albino) were exposed to: TINOX at 4.2 mg/M³; DIMETHOATE at 16 mg/M³, WOLFATOX at 0.8 mg/M³ singly and together by inhalation for 8 days. Histology eg of lung and thyroid; histochemistry eg of liver enzymes; and morphometrics eg of thyroid and ¹³¹I uptake and metabolism in thyroid were measured. In addition to the single or combined pesticides, the animals were exposed to HEAT at 35° C at the same time. The organophosphates given in a high temp environment resulted in a higher fatty degeneration of the liver, decreased non-specific esterases and succinic dehydrogenases, an increase in acid phosphatases and drop in thyroid wt. Action of Tinox + heat was the most striking.

## Key Words

organophosphates, heat, combined stresses, liver function, toxicology, Tinox, Dimethoate, Wolfatox, insecticides, interactive responses

## Notes

Title continued: "... 2. Histological, Histochemical, and Morphometric Studies" (Ger)
Effects of Exposure to Acrolein Vapor in Hamsters Simultaneously Treated with Benz(a)pyrene or Diethylnitrosamine

In laboratory experiments, hamsters (252 M, 252 F, age 6 wks) were exposed to: ACROLEIN vapor, 4 ppm, by inhalation 7 hr/day, 5 day/wk for 52 wks; and either DIETHYLNITROSAMINE (DENA), total dose of 2.1 \( \mu \)L 1 x/3 wk for 52 wks; or BENZO(A)PYRENE (BP), at 18.2 or 36.4 mg, 1 x/wk x 52 wks, with DENA or BP instilled intratracheally. Treatments involved combinations of A with BP or DENA. The subjects were studied at 81 wk for incidence of respiratory tract tumors. Acrolein alone caused growth retardation, hyperplasia of nose, temporary behavior changes, irritation of nose and eyes, hepatic cysts, testicular atrophy, some amyloidosis, kidney changes, but with no effects on carcinogenesis itself, nor on blood chemistry or hematology. Some hyperplasia in nose was noted. DENA caused respiratory tract tumors like A. BP + A produced only slightly higher incidence of BP tumors in the respiratory tract, with latent period shortened by A, which has cocarcinogenic effect.
Asthma due to Inhaled Chemical Agents—Epoxy Resin Systems Containing Phthalic Acid Anhydride, Trimellitic Acid, and Triethylene Tetramine

Fawcett IW, Taylor AJ, Pepys J

ENGLAND: Brompton Hosp; Nat Heart & Chest Hosp.

Clin Allergy 1977; 7:1-14

In laboratory study workers with occupational asthma were exposed to fumes of certain epoxy resins (phthalic acid anhydride, triethylene tetramine, toluene diisocyanate, trimellitic acid. These substances induced immediate asthmatic reactions.

epoxy resins, additives, combined stresses, phthalic acid anhydride, trimellitic acid, triethylene tetramine, asthma, dermatitis, pulmonary pathology, interactive responses
A large group of thermal decomposition products from synthetic and natural polymers were screened. These products include: substances from polyurethane, polystyrene, isocyanate, phenol-formaldehyde, cellulose fiber, teflon, wool fibers. Thermal decay was done in a Lindbergh furnace heating the candidate materials to $600^\circ C$ to simulate some fire conditions. The effluent from the furnace was cooled with air, and used to expose mice (M Swiss, arranged for head exposure only), to irritants for 10 min/test. Toxicity of these products depends on their decomposition temperature.
In an occupational study of machine tool operators and other workers (77 M & F, employed over 10 yrs), they were exposed to aerosols of lubricating oils, and sulfate coolants. Measurements of pulmonary function included vital capacity, max ventilation, and gas exchange. Chronic exposure to these substances produced decreases in max ventilation and vital capacity, and increases of oxygen consumption as a function of duration of exposure. The etiology of occupational lipid pneumonia, and the inhibition of phagocytosis under these stresses are discussed.

Key Words:
- lubricating oils, aerosols, workplace exposures, combined stresses, machine tool operators, pulmonary functions, pneumonia, interactive responses
In laboratory studies rats (albino) were exposed to: THERMO-OXIDATION PRODUCTS from degradation of Hydrocarbons, at doses of 200, 300, and 410 mg/M³; also machine oil aerosols (doses not given). Exposure was 5 hr/day for 6 mo to single and combined substances. Each stressor appeared to have marked toxic effects: with drop in blood pressure, cardiac a-v conductivity, oxygen consumption, inhibition of neutrophil phagocytic activity, decrease in activity of certain tissue enzymes, and inhibition of certain immunological reactivity in test animals. The thermo-oxidation products enhance the toxic effect of the oil aerosol in combined exposure. No other data are available.
In laboratory studies mice (M. albino) were exposed to a mixture of volatile products of thermal oxidation of greases. (No data were given on modes of production, components and their concentration.) Exposure was at 2 hr/day, 5 days/wk, for 1.5 mo by inhalation. After 1.5 mo of chronic exposure, the animals were given exposure to the volatile products at LC$_{50}$ concentration (not specified) in a single 4 hr dose. Measurements included cholinesterase activity, RBC, hemoglobin level, and certain aspects of behavior. No other data are reported.
In laboratory studies rats (M) were exposed to: VINYL CHLORIDE MONOMER (VCM) in air containing conc of 0.5, 5.0, 10.0 % VCM for 6 hrs; or in a variant, at 0.05, 5.0 & VCM for 6 hrs or 5 days. (VCM is used in plastic plants to make eg polyvinyl sheeting). Rats were pretreated with PHENOBARBITAL Sodium 0.1% in drinking water, starting 7 days before VCM. The dose of 100 mg/Kg/day is able to double Cytochrome P-450 and oxidative N-demethylase activity. These enzyme inductions can activate other halocarbons into hepatotoxicity. VCM alone (10%) initially increases activity of AKT (alanine-alpha-ketoglutarate transaminase) or SDT (sorbitol dehydrogenase. Pretreatment with PB + 5% VCM enhances the liver enzyme lesions, causes vacuolization of centrilobular parenchymal cells, jumbles of smooth endoplasmic reticulum, and focal necroses. With chronic dose (5 d) of VCM no further enzyme changes occur.

Initial exposure to the toxic protects somewhat against reexposure.
In occupational observations the nature of iron foundry worker exposure to known carcinogens and cocarcinogens was explored. Foundry air/dust samples analyzed for polycyclic aromatic hydrocarbons (PAH) detected over 200 compounds; 50 were identified as PAH, including Benzo(a)pyrene (BAP). The latter was highest where pitch was used as the organic additive in molding sand; where BAP at 5.1 µg/m³ was 50x that case where coal powder was used as the additive. The PAH variants are formed and released in extreme conditions of casting: 1400°C, high pressure, limited oxygen supply. The Ames assays on dust showed mutagenic activity, but lower than BAP, which can be used here as a hygienic marker.
In laboratory studies, dogs, rats, mice were exposed to: 30 nitrotoluene analogs as found in CW (condensate waste water). A blend of these substances was suspended in acetone and mixed with suitable vehicle for oral ingestion. Dosage was carried to LD_{50} in single doses. For rats, these levels were: 447 mg/Kg (M) and 295 mg/Kg (F). Another series of repeated doses was done: for dogs 0.05, 0.5, 5.0 mg/Kg in a capsule/day x 26 wk; and in rats/mice 0.001, 0.1, 0.1 % of this mix, for 4 or 13 wks. There was produced compensatory anemia with reticulocytosis (severe in rats). Heinz body formation (common feature of nitrotoluene toxicity) was seen, other blood cell changes, pigments in liver cells, atrophy and aspermatia in testes, hyperplasia and inflammation in repro organs, neurotoxic signs at high doses. In rats & mice, drop in food intake, body and organ wts; 2,4 & 2,6 dinitrotoluene the chief causes of toxic effects.
Asbestos and Lung Cancer: An Analysis of the Epidemiological Evidence on the Asbestos-Smoking Interaction

Three concepts for asbestos-smoking interaction on human lung cancer production are discussed:
Excess incidence of lung Ca independently due to asbestos and smoking would be added together when both are present (additive).
Addition of each one of the two agents produces an increase in lung Ca incidence proportional to the effect of the other (multiplicative model).
Asbestos could only increase lung Ca in the presence of smoking (promotor model).
The additive model appears to the author the least plausible, from the data. The multiplicative model is consistent with multistage carcinogenic discrete-hits mechanisms; each factor can produce human lung Ca and act synergistically. Many studies are not comparable, are different in design, exposures, criteria, samplings.

smoking, asbestos, combined stresses, lung cancer, chrysotile, epidemiology, interactive response models
**Role of Infective, Immunological, and Chronic Irritative Factors in the Development of Silicosis**

In laboratory studies rats (220 SD pathogen-free) were exposed to: SILICA, Tridymite, particle size 1-2um, 50 mg in saline, intratracheally, 1 time; also ANTIGENS, horse ferritin at 25 mg, or horseradish peroxidase at 0.25 mg, inhaled, as immunological stressor factor; also INFECTION in these pathogen-free rats, by exposure in usual cages to endemic bacterial flora; also OZONE at 2 mg/m³ 8 hr/day 5 days/wk for 6 or 12 mo, as irritant factor. With tridymite, in 3, 6, 12 mo granulomas (not silicosis) develop, without confluence or hyalinosis. If they are put into the infective environment after TD growths will be faster, more numerous, and silicotic. Exposure to O₃ also increases infection incidence so increases silicosis. Ferritin and peroxidase stimuli in the pathogen-free have no effect on development of silicosis. Bacterial flora are the major accelerators of silicosis here.

**Key Words**
- silica, infection, irritants, combined stresses, silicosis, pathogen-free animals, bacterial flora, peroxidase, ferritin, ozone, granulomas, interactive responses
The mixes of mineral exposures encountered in various occupations are discussed. Coal miners drilling rock may develop silicosis-anthracosis (sometimes called anthrosilicosis). Hematite miners and workers in iron foundries may develop siderosis-silicosis. Others get argyria-silicosis. In one unusual specific case, a patient, a metal worker and mold maker for BeCu ingots, was exposed also to talc and asbestos. He was also a smoker. After 6 yrs of pulmonary insufficiency, cyanosis, FEV 20% of normal and VC 33% of normal and death at age 48 yrs, his tissues showed not only silicosis nodules but talc crystals, asbestos, and beryllium deposits. Be itself gave an underlying lymphocytic or granulomatous inflammation and interstitial fibrosis, sometimes without visible particles in lung tissues.

**Keywords**
silicosis, asbestosis, pneumoconiosis, talcosis, berylliosis, lung pathology, combined stresses, interactive responses

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**Chest 1979 (6);75:726-728**
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<td>In an occupational study (with limited data presented), workers (47, ages 21-50 yrs, were exposed 1-30 yrs to environments in open hearth steel smelting. Specific stresses encountered in combination include: SOUND (noise to 97 dbA), HEAT with high relative humidity, DUST approx 25 mg/m³, METALS and their oxides, including Mn, Cr, V, Mo, and GASES, including CO and CO₂. Measurements were made of blood pressure, pulse rate, muscle strength, physical endurance, oculomotor reflexes, attention, etc. It was indicated, without detailed explanation, that occupational exposure to these factors degraded working ability.</td>
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Biochemical and Cellular Effects of Welding Fume Particles in the Rat Lung

In laboratory experiments rats (160) were exposed to welding fumes. Materials from manual metal arcs (eg Ni, Cr, gas & oxide mixes); and from arcs with stainless steel flux coated electrodes (basic & rutile, & incl. Cr, Ni, Mn, Fe, Cu, SiO₂, Ti, etc.) were collected on filters, yielding particles with sizes 90% under 1.5 um, suspended in saline, and instilled intratracheally and IP at 1, 5, and 10 mg. Materials from the Manual Metal Arc caused changes in pulmonary surfactant and hydrolytic enzymes, and changes in lung wt/body wt. In cytotoxicity, stainless steel was more active than basic coatings or rutile, and TiO₂ caused no wt change. SS increased abnormal cells, surfactant, and changed lysosome level.

welding fumes, combined stresses, manual metal arc, toxicity, interactive responses
### Study of Pulmonary Deposition, and the Elimination of Some Constituent Metals from Welding Fumes in Laboratory Animals

In laboratory studies, guinea pigs (250-350 g) or rats (M, SD, 200 g) were exposed to welding fumes. Materials from manual metal arcs or metal-inert gas welding (with stainless steel wire) included various conc of Fe, Co, Ni, Zn, Sb, Cr, with particle sizes 0.06-0.1 um. These particles were inhaled for 46 or 256 min. fume conc av 1178 mg/m³. Analysis was made at various times after exposure of deposition of particulates in lungs, and the rate of metallic component removal from lung tissue. This rate of elimination appears to depend on solubility of the specific metal. Particles were also radiolabeled for lymph clearance studies. No combined effects were evident.

**Key Words**
- welding fumes, combined stress, arc welding, gas welding, lung pathology, chromium, cobalt, iron, nickel, zinc, interactive responses
Worker Exposure to Chemical Agents in the Manufacture of Rubber Tires and Tubes: Particulates

In occupational studies on rubber workers in 14 tire plants, exposure to particulates such as CARBON BLACK, SULFUR, TALC, MICA, SOAPSTONE, RUBBER FUMES, ZINC STEARATE, ANTIOXIDANTS, OIL DROPLETS, ACCELERATORS, etc. were considered. Analyses of exposures included work with 12 occupational classes, consideration of specific processes and their related environments (e.g., compounding, milling, mixing, curing, finishing, calendaring, extrusion), and the collection of material with area samplers, and respirable-material personal samplers. There was special interest in any fluxes of benzo-a-pyrene and capture by particulates. Exposure levels further depended on ventilation and work practices. Measurements were made of work-related illness and mortality. Methods of control of environment are discussed.

particulates, combined stresses, rubber workers, toxicity, carbon black, antioxidants, sulfur, talc, mica, soapstone, rubber fumes, zinc stearate, accelerators, milling, plant processes, work-related illness, interactive responses
In laboratory experiments, hamsters (M, F, Syrian) were exposed to BENZO(A)PYRENE at 2 or 3 mg; together with either MAGNESIUM OXIDE at 1 mg or IRON OXIDE at 3 mg, BAP+MgO or IO were instilled intratracheally as fine mixed particles. BAP + MgO caused changes in squamous cell carcinomas in larynx, (with latent periods as short as 9 wks) also tracheal adenocarcinomas and bronchial lesions enhanced. MgO enhanced the tumor inducing effects of BAP; FeO was equally effective, but acts more on lower bronchial tree. Both FeO and MgO were effective as carriers. The action of the carrier agent does not depend on physical or chemical properties of the dust, which affects not only absorption and retention, but pulmonary defense mechanisms, mucus secretion, cilia function.

**19. KEY WORDS**

benzo(a)pyrene, magnesium oxide, iron oxide, combined stresses, carcinogenesis, lung pathology, laryngeal neoplasms, interactive responses
In laboratory experiments mice (albino) were exposed to FORMALDEHYDE, or NITRIC ACID FUMES, OR ACROLEIN (doses not avail) as inhalation irritants; together with AEROSOLS (incl. glycerin, triethylene glycol, ethylene glycol, mineral oil, dicalcite, celite, NaCl, attapulgus clay, santocel, etc) by inhalation. Formaldehyde is an irritant to the upper respiratory passages, and acrolein is irritant to upper and lower tree. Aerosols increased toxicity of formaldehyde but had no effect on toxicity of nitric acid fumes. Data are provided showing changes in survival times when aerosols are added. The interactions depended on the relative penetration of particles and vapor molecules.
Asbestos Exposure, Smoking, and Neoplasia

Selikoff IJ, Hammond EC, Churg J

Mt Sinai Hosp Dept Community Med NY NY

1968

JAMA 1968 (2);204:104-110

In occupational observations on asbestos insulation workers (approx 370) with data from 1922-present obtained for Newark and NYC experience,from records on members of Intnl Assn of Heat & Frost Insulators and Asbestos Workers (union), analyses were made of mortality. These workers have a risk 7-8x the unexposed of dying from bronchogenic carcinoma (BC). Asbestos workers who smoked had 92X the risk of dying from BC compared with non-smoker non-workers. Mesothelioma risks were 10x the non-exposed. "Light" exposure is fallacious, autopsies world-wide have shown asbestos bodies in 25-50% of such groups.

asbestos, smoking, combined stresses, neoplasia, epidemiology, interactive responses
**Title:** A Health Survey of Granite Workers in Finland

In occupational observations, workers (1037, avg age 36.5 yr) in 71 granite plants, were exposed to a variety of stressors associated with the specific process: refining (shaping, cutting, dressing with dust, noise, vibration, in 1 yr exposures); loading; crushing and grinding (sand, dust, noise); quarrying; drilling; transportation, dressing with pneumatic & other hammers (with dust, noise, vibration, flying fragments); sawing; smoothing/polishing; and sandblasting. From these the composition and levels of exposures were estimated. Health indicators included: subjective, chest x-ray (for tuberculosis, silica, fibrosis, tumors); audiometry; respiratory function; neurology. Present work methods in this industry increase risk of respiratory illness, hearing loss, vibration disease. Highest risks are: drill, dress, refine, sandblast. X-rays show highest fibrosis in dressing, sandblasting, drilling. Other discussions of vibration syndrome and silicosis are found.

**Key Words:**
- granite work, silica, dust, combined stresses, toxicity,
- respiratory pathology, vibration syndrome, hearing loss,
- fibrosis, interactive responses

**Notes:**
***Title Continues: "...Radiographic Findings, Respiratory Function, Hearing, Electric Sensory Thresholds of the Fingers, and Subjective Symptoms"
In laboratory experiments, rats (M Wistar, pathogen-free) were exposed to: COAL DUST at approx 6-15 mg/m³ (incl 2-6 mg/m³ soot) also DIESEL EXHAUST from engine operated in 2 different modes, at 8.3 mg/m³ (incl 2 mg/m³ soot); given singly or in combination for 20 mos. Measurements were made of body wt, COHb, with other observations of lung pathology, hematology, mortality. There were exposure-related lesions from these stressors, resembling coal workers pneumoconiosis, but no changes in weight, mortality, or blood, except COHb which rose.
PARTICLES

COMBINED STRESS EXTRACTS
A variety of effects, and examples of specific substance actions discussed include: modulation of polynuclear hydrocarbon (PNH) action especially in tumor induction, by diet, enzyme-altering agents, dosage vehicles. A spectrum of PHC (aromatics) from auto exhaust (including non-carcinogens influencing tumor induction) is given. Tumor accelerating substances in cigarette smoke are considered. The pronounced cocarcinogenic effects of catechols and non-carcinogens, and data showing inhibiting effects of 9 hydrocarbons found in urban air are presented. It is stated that most naphthalenes in cigarette smoke have inhibitory effects on skin tumorigenicity by BaP (xc for several naphthalenes). Antioxidants as inhibitors of tumor induction with certain agents are also considered. The empirical complementarity of these various agents is discussed at length.

**KEY WORDS**

polycyclic hydrocarbons, auto exhaust, cigarette smoke, combined stresses, carcinogenesis, benzo(a)pyrene, dibenzanthracene, naphthalenes, antioxidants, cocarcinogenesis, interactive responses

**NOTES**

** This is one chapter from the Proceedings of a Symposium on Health and Ecological Assessment of Polynuclear Hydrocarbons; published in this journal issue (365 pp, 540 refs)
Absence of Synergism between Exposure to Asbestos and Cigarette Smoking in Asbestosis

Occupational exposure and clinical data were obtained on 4 groups of workers in different plants, including two shipyards. (Total pool was about 400, ages 41-45 yrs). Questionnaire sought data on respiratory symptoms, cough, sputum, and job history, and pulmonary function, physical exam, and chest x-rays were done. Exposures were to ASBESTOS (in pipe covering and filter work) (data not available) and CIGARETTE SMOKING. Exposure to the A ranged 3.4-11.6 yr. The incidence of lung cancer in A + S workers was far greater than expected for smoking alone, but the synergistic role in fibrosis development itself has not been established. Synergism between the A and S exposures is not present for manifestations of asbestosis (fibrosis).
Occupational and clinical studies were made on workers (10,900 M, 500 F) who worked more than 1 mo in the mines and mills of Asbestos and Thetford, Quebec; during 1910-1975. Data sources included a 1966 register of 30,000 (nearly everyone) ever employed in the chrysotile industry; the ICD was used, and dust concentrations were estimated and summed up. Smoking exposure was also queried and estimated. Of this sample, in 1875 4460 M and 84 F had died. Trends in total mortality, lung cancer, pneumoconiosis were set down as functions of exposure and were linear for the latter 2. Excess mortality was 10% at Thetford and 2% at Asbestos Quebec, under conditions of study, and were worst if workers were employed over 20 yrs.

**Key Words**

- dust
- asbestos
- smoking
- combined stresses
- chrysotile mining
- pneumoconiosis
- lung cancer
- interactive responses
**Title:** Effect of Hot Microclimate on Development of Pneumoconiosis (Rus)

**Authors:** Zinger FH, Sukhanov VV, Sorokin FS, Zemliakova LF

**Publication:** Vrach delo (USSR) 1978 (1);125-127

**Abstract:**

In laboratory studies rats were exposed to COAL DUST at 20 mg intratracheal; also HEAT at 350 C and 85-90% RH 4 hr/day, 5x/wk. In one treatment, CD + H were applied for 8 hrs. Heat enhanced the formation of collagen in CD + H (measured by oxyproline content in the lung). HEAT inhibited pulmonary fibrosis during the first 4 hr of experiment (a period of adaptation) and the enhanced development of fibrosis during the late stages of exposure. In other studies of Donbass coal miners (deep and shallow) exposed for 15 yrs, the incidence of pneumoconiosis was higher in the deep mine with higher temperatures, than in the shallow mines.

**Keywords:** dust, heat, combined stresses, coal mines, pulmonary fibrosis, interactive responses

**Report Date:** 1978

**Number of Pages:** 3P 5R

**Security Class:** NOT

**Distribution:**

**Key Words:**

dust, heat, combined stresses, coal mines, pulmonary fibrosis, interactive responses
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<td>Kibelstis JA, Morgan EJ, Reger R, Lapp NL, Seaton A, Morgan WK</td>
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In an occupational study in workers in 32 bituminous coal mines (anthracite not included), with emphasis on dust exposure with two particle size clusters (0.5-5.0 um, which is involved in pneumoconiosis, and 6-15 um) other data assembled included physical exam findings, chest radiographs, pulmonary function, and response to questionnaire. The prevalence of bronchitis (with cough, phlegm) was higher in smoking miners than among non/ex smokers. Surface workers showed less bronchitis. Airway obstruction was higher among those from work at coal face, compared with surface work. The effect of smoking was 5x that for coal dust.

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<td>coal mining, dust, smoking, combined stresses, epidemiology, pneumoconiosis, interactive responses</td>
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DD FORM 1 JAN 73 1473 (MOD.)
Chronic Bronchitis in Miners and Non-miners: an Epidemiological Survey of a Community in the Gold-Mining Area in the Transvaal

Sluis-Cremer GK, Walters LG, Sichel HS

Gold-mining, smoking, combined stresses, dust, air pollution, lung pathology, toxicity, interactive responses
In an occupational survey of ZINC and LEAD miners, vital statistics were obtained in Zn-Pb mining towns. In the case-referent study, including 29 subjects who died of lung cancer, 21/29 had been exposed to this underground mining. SMOKING habits data were also gathered. The incidence rate for lung cancer among miners is 16X non-miner rate. Non-smokers may be more apt to develop lung cancer than smokers among these miners. The radon daughters include alpha emitters, whose dose to potential tumor cells depends on their penetration; this is influenced by thickness of the mucus sheath eg in lung tissue. In smokers, this sheath will be thicker, and could cut dose by 50%. But in smoker-miners who get cancer, the induction-latency period is much shorter; and smoking may have a promoter effect after radiogenic induction.

**Key Words**
- mining, smoking, combined stresses, lead, zinc, radon daughters, alpha radiation, bronchitis, lung cancer, interactive responses
In an occupational survey of uranium miners in selected areas, and considering exposures which alter pulmonary function (silica dust, radiation, aging, cigarette smoke, and which are concurrently operative during career exposure; there was highlighted in this study the RADON DAUGHTER exposure. This was calculated by correlating RD measurement in the mines (cumulated as "Working Level Months") of intensity and duration, with data from death certificates (and autopsy and histology) also using modified life tables. Smoking is viewed by some as a promoter in the development of cancer induced by other agents, also acting to reduce the length of latent period to onset. Here, smoking was seen to contribute to lost ventilation function in U miners. Respiratory cancer rates in U miners (S and non S) was 6-9X that for non-miners (with similar smoking habits). The principal Ca agent is radiation; S is then a cofactor or promoter, not synergistic.

key words:
uranium mining, smoking, combined stresses, radon daughters, silica dust, cancer promoters, pulmonary pathology, interactive responses
In laboratory studies dogs (M & F, ages 2–2.5 yr, beagles) were exposed to: RADON DAUGHTERS at 105 nCi/L + URANIUM (carnotite ore dust) at 12.9 mg/m³; also CIGARETTE SMOKING via mask, at 10 cig/16 hr day, over 4.5 yr. In general, smoking has a mitigating effect on RD induced respiratory tract cancer in dogs.

Emphysematic fibrosis was more prevalent and severe in mixed exposure. There was no apparent effect here of RD &/or smoking on life-shortening.
In a survey associated with this group's programs in multiphasic health screening, subjects (about 70,000, 15-79 yrs) were queried on their present and past occupational exposures to chemicals, fumes, sprays, dusts, radiation, heat, noise, and various hazards encountered separately or together; with any available information of the frequency and extent of exposure. Smoking history was also recorded. Smokers were more apt than non-S to report previous and recent occupational exposures to chemicals, solvents, cleaners; NH₃, Cl₂, O₃, NOₓ; engine exhaust; plastic/resin fumes; metal fumes and sprays; asbestos and cement grains; silica and rock dust. There was no difference in frequency of reporting exposures between S/non-S for insect and plant sprays or ionizing radiation.

- Smoking, occupational hazards, combined stresses, toxicity, dust, noise, radiation, heat, toxic chemicals, tracheobronchial irritation, interactive responses
In laboratory experiments hamsters (59, Chinese, ages 10-20 wks) were exposed to controlled SMOKING (S) with Borgwald smoking machine, which uses 5 at a time, and uses 30 cigarettes/hr, with smoke diluted to desired CO levels using CO monitor to levels of 330-440 ppm. Smoke exposure was for 1 hr/day. ETHANOL at 10% (other data unavail) was given during wk 1, at 15% during wks 2 & 3, and 20% for rest of 12 wks. Various treatments with E + CS were used. After 12 wks, bone marrow cell studies showed no chromosome aberrations, or sister chromatid exchanges, or chromatid breaks or translocations. However, there was seen high mitotic activity in smoke-treated animals.
The Combined Effects of Smoking and Occupational or Urban Factors in Relation to Lung Cancer.

Waller RE


16. EXTRACT

Occupational epidemiological studies here considered exposures in various OCCUPATIONS: Uranium, Nickel, or Gas working; to EXTERNAL ENVIRONMENTS comparing N.Wales, regarded as unpolluted, with Merseyside, considered polluted; and combined with SMOKING. The effect of combinations of these factors on lung cancer mortality was studied. In some occupational groups (U and Ni work), smoking enhances lung cancer risk. In general populations, the effect of smoking is large relative to other factors. There was no indication in this study of interaction between smoking and air pollution. Air pollution, either alone or with smoking is asserted to be a minor factors in the development of lung cancer.

19. KEY WORDS

occupational hazards, environmental pollution, smoking, combined stresses, uranium industry, nickel working, gasworking, lung cancer, interactive responses
Evidence of a Multiplicative Effect between Cigarette Smoking and Occupational Exposures in the Etiology of Bladder Cancer

Case and control studies were made in Torino province, on 225 case-referent pairs, in OCCUPATIONS with excess risk for cancer, including dyestuffs manufacture, rubber & cable production, leatherwork, petroleum refining, textile industry, etc. CIGARETTE SMOKING exposure was also recorded (it was noted that 30 unfiltered cigarettes/day will expose to 3 mg of 2-naphthylamine in a 2 yr period. There was found a clear cut dose relation between smoking and risk of urinary tract cancer; at different smoking levels + one of the occupations, the risk form suggested a multiplicative effect, resembling the asbestos + cigarette smoke association with lung cancer.

smoking, occupational e: sure, combined stresses, dyestuffs industry, leatherworking, textile mills, petroleum refining, furnace working, chemical industry, rubber & cable production, cancer, lung pathology, urology, interactive responses
The Interaction of Air Pollution, Occupation, and Cigarette Smoking as Risk Factors in Lung Cancer

Vena JE

Roswell Park Memor Inst
Buffalo NY

Am J Epidemiol
1981;109:441 (abstract)

This epidemiology presentation considers two groups: lung cancer patients (417 M) and referents (752 with non-respiratory, non-neoplastic diseases) as seen at RPMI. Exposure to PARTICULATES in air was estimated, using available Total Suspended Particulate data, and local histories of problem point sources. SMOKING habits of the subjects were also recorded. When air pollution, occupation, and smoking are considered separately, smoking is the strongest individual risk factor, extending risk by 6X over non-smokers, for lung cancer. There was no support for the thesis that exposure to air pollution alone increased risk. Risks seemed synergistic for: heavy smokers + heavy occupational exposure; heavy smokers + heavy air pollution; and smokers + occupational exposure + air pollution (aggregate risk factor 7X base, with "Rothman Index of Synergy" 2.16. Occupations were not discussed.

air pollution, smoking, combined stresses, lung cancer, particulates, occupational hazards, risk factors, synergy indices, interactive responses
An Industrial Study of the Biological Effects of Cotton Dust and Cigarette Smoke Exposure

Merchant JA, Lumsden JC, Kilburn KH, O'Fallon WM, Ujda JR, Germino VH Jr, Hamilton JD

Duke Univ Med Ctr, Durham, NC

J Occup Med 1973 (3);15:212-221

Occupational and clinical observations were made on textile mill workers (846 M) exposed to COTTON DUST at 0.5-2.1 mg/m³ "lint free", for up to 25 yrs. The exposures were sampled every 50 ft in breathing zones of workers, and were highest in preparation areas of these cotton blend mills. The second stressor considered was SMOKING, classed as "never" (for at least the past 1 yr), or moderate (1-20 cigarettes/day used up to 1 mo before sampling), or heavy (more than 20/day). Cigarette smoking interacted with CD exposure to increase byssinosis prevalence and severity. Byssinosis symptoms are classed as: Grade 0, no cough, but tightness in chest with breathing; Grade 1, tightness in chest and breathing difficulty; and Grade 3, these symptoms + other deterioration in pulmonary sufficiency (dyspnea, changed ventilating capacity). Cigarette smoking also increases the overriding bad effects of CD on 4 measures of ventilation capacity; bronchial clearance drop.

cotton dust, smoking, combined stresses, textile mill workers, byssinosis, pulmonary pathology, cigarettes, interactive responses.
MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A
GAS/VAPOR

COMBINED STRESS EXTRACTS
This report was presented at a symposium on health effects of indoor air pollution. It discusses the principal sources of fire toxics (seating, bedding, etc), the initiation event (smoking, electrical fault, heating, flammables), the principal toxic components in everyday fire exposure (including HCN, CO), the levels found, and those necessary to incapacitate or kill; including the modulating effect of body alcohol levels. The pathology of fire toxic effects is considered, highlighting pulmonary edema and congestion, burns, soot deposits, raised COHb. Sources of heavy metals from paints and plastics, and of other toxics are considered. Interactive events are given attention.

**Key Words**: fire toxics, combined stresses, hydrogen cyanide, carbon monoxide, carboxyhemoglobin, heavy metals, smoke, soot, burns, interactive responses

**Notes**

**Publication**

Bull NY Acad Med
1981 (Dec); 57:997-1013
**Health Effects of Coal Mining and Combustion: Carcinogens and Cofactors**

**Falk HL, Jurgelski W Jr**

**Environmental Health Perspectives** 1979 (12); 33:203-206

Among the exposure factors discussed here are: polycyclic and heterocyclic compounds (present in soot and coal), free radicals from combustion, nitrosamines, some inorganic compounds containing As, Cd, Pb, Se. There is discussion of the ways in which actual synergy, cofactor operation, cocarcinogenesis may be obscured by the time-lags and extraneous factors entrained in these processes. The augmentation of inhalation toxicity by substance linkup with particulates is considered. There is a survey of the epidemiologic evidence of carcinogenic risks in mining, and an adversary discussion of the way in which lab studies support or contradict epidemiologic data. Topics of prevention of exposure or reduction of hazard are discussed.

**Key Words**

- coal, polycyclic hydrocarbons, combined stresses, soot, metals, arsenic, cadmium, lead, selenium, nitrosamines, cocarcinogens, interactive responses
In a laboratory study mice (400 F, age 2 mo) were exposed to: IONIZING BETA RADIATION from 90Strontium medical applicator, at 86 R equiv Beta/sec at the surface (back of mouse), for total dose of 2,000 Rep(Dose drops to 1% at 5 mm skin depth). Exposure was for 2 sec, 2x/wk or 12 sec, 1/mo. They were also exposed to CIGARETTE TAR from an autosmoking machine. The nicotine fraction was removed, and the tarry residues, in acetone painted on shaved backs 3x/wk for 12 mo. Effect on epidermal carcinogenesis was additive, with no evidence of synergy; this radiation had very little carcinogen skin effect. In one group, 61% developed skin cancer from tar at 3x/wk and 200 Rep 3 x/wk. There are, in other experiments with X-rays and methylcholanthrene, additive and synergistic effects in development of leukemia in mice.

**Key Words:**
cigarette tar, beta radiation, combined stresses, strontium-90, bronchogenic carcinoma, carcinogenesis, interactive responses
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<td>In survey of exposures in asbestos and cement works to dust and other hazards, a variety of confounding factors are considered. There is difficulty in standardizing for age in regression graphs; for many indices smokers have worse lung function with age, changing non-linearly; eg FEV drops 10x faster in smokers vs non-smokers, and smokers present with lower FEV than non-smokers. The report claims that using this measure, the age-smoking habits interaction entirely accounts for apparent synergism in smoking and dust exposure. Cigarette smokers + dust have worse lung function than non-smokers, and gap gets wider with increasing dust dose or duration of exposure.</td>
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DD FORM 1 JAN 73 1473 (MOD.)
In occupational studies in Rotterdam and Amsterdam streets, these groups of human subjects were observed:

- traffic police, 36 non-smokers, exposed to exhaust for 1-4 hrs in Rotterdam; traffic police, 10 non-smokers 4.5 hrs duty in Amsterdam; traffic police, 14 smokers in Amsterdam; drivers (cabs, vans) 7 hrs city driving, non-smokers; cyclists, 13 and moped, 8 drivers; customs officers, 13, non-smokers. In Rotterdam, COHb before work at 0.93%, then up to 1.1% after. In Amsterdam, levels rose from 1.43 to 1.74 in non-smokers, from 4.62-4.91 in smokers, for drivers from 1.9 to 2.15%, for cyclists no change, for customs officers a rise. These conditions were for 1967, and change year by year. COHb at 5% would cause early signs of intoxication, and would need exposure to 30 ppm CO. Tunnels go up to 100 ppm. Other factors: aldehydes, SO2, soot were not studied at this time.

**Key Words**
carbon monoxide, vehicle exhaust, combined stresses, toxicity, motor traffic, air pollution, carboxyhemoglobin, interactive responses
**Marked Lethality of Rats in Combined Exposure to Carbon Monoxide and Diethyldithiocarbamate**

In laboratory studies rats (39) were exposed to:
- CARBON MONOXIDE up to 1000 ppm for 2.5 hr; also DIETHYLDITHIOCARBAMATE (DDC) at 0.5 g/Kg (a superoxide dismutase inhibitor, used in O₂ toxicity intervention, and well below LD₅₀ here).
- CO + DDC killed 16/23 rats. DDC had no such action. CO alone reached an equilibrium conc with COHb of 60%. No other data given.

**Key Words**
carbon monoxide, diethyldithiocarbamate, combined stress, toxicity, superoxide dismutase, interactive responses
In laboratory studies rats (15M Wistar) were exposed to: CARBON MONOXIDE at 100 ppm; also DICHLOOROMETHANE at 1000 ppm, in 3 hr exposure alone or in combination. Observations were made of kidney and liver microsomes, blood COHb, ethoxycoumarin-o-diethylase activity. Effects of combined exposure are additive, and COHb increases after this exposure. DCM yields CO in the body, to the blood, then equilibrating with alveolar air.

**Key Words**
carbon monoxide, dichloromethane, combined stresses, toxicity, carboxyhemoglobin, liver enzymes, kidney enzymes, interactive responses
In this study of conditions encountered by locomotive repairmen, and other related shop and yard workers, volunteers were exposed to DIESEL EXHAUST for up to 1 hr, from 1 cylinder 4 cycle engine, with inhalation and face exposure. Composition of the exhaust was typically: NO\textsubscript{2} 1ppm, SO\textsubscript{2} 0.2ppm, CO under 20ppm, CO\textsubscript{2} 1000ppm, total aldehydes under 1ppm, acrolein under 0.05ppm, formaldehyde under 0.1ppm. No effects were seen in measured pulmonary resistance (from esophageal pressure and flow) for exposures up to 1 hr. Modes of exposure were not stated.
**In laboratory studies rats (M albino) were exposed to:**

**CARBON MONOXIDE; SULFUR ANHYDRIDE, NITROGEN DIOXIDE, AND AMMONIA** (values not given), with doses of individual or mixed substances, in 5 min exposure. (This is in part, a simulation of the mixture of combustion products from a heated (T 850°C) synthetic grease). Five min exposure to a combustion product mix gives a greater toxic effect than CO exposure alone, in the same conc as in the mixture. All animals survived exposure to CO alone, compared with 25-30% lethality from the mix. Oxygen content did not affect toxicity of the combustion products.

**Key Words:**

- carbon monoxide, combustion products, combined stresses, sulfur anhydride, nitrogen dioxide, ammonia, aerosols, toxicity, interactive responses
In laboratory studies mice (M albino) were exposed to: NITROGEN DIOXIDE, AMMONIA, SULFUR COMPOUNDS and other volatile gaseous products of combustion of synthetic grease (heat to 850°C in air) (values not given), in 5 min inhalation exposure. Lethality in 3 days and COHb content were observed. Discussion follows on the toxicity of the components and of the mixtures, at different exposure rates.
In laboratory studies rats (M, albino) were exposed to: SODIUM NITRITE at 0.2-0.4 M/kg IP; also CUBON MONOXIDE at 1.2 mmol/kg sc; also CARBON TETRACHLORIDE at 8.3 mmol/kg po. These were given separately or in combination. NaNO₂ alone drops motor conduction velocity; associated with the formation of MetHb. MCV change starts at 16.7 MetHb, is distinct at 22%. CO drops MCV starting at COHb 30-50%, yielding MCV drops of 24% and 28%. CO and NaNO₂ have approx similar modes of action, shifting dissociation curve of O₂-Hb to left. CCl₄ did show differing effects on impairment of nerves. There were no differences between CCl₄ + CO and CO alone. A single admin of NaNO₂ or CCl₄ has no influence on CO-induced changes of MCV. Additional toxic substances cannot exaggerate this effect. There are no apparent antagonistic or potentiating effects among NaNO₂, CCl₄ and CO.

19. KEY WORDS
carbon monoxide, sodium nitrite, carbon tetrachloride, combined stresses, nerve conduction velocity, interactive responses
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<td>16. Extract</td>
<td>In laboratory studies human subjects (28M, 28F, healthy students) were given VITAMIN E at 800 IU dl-alpha-tocopherol/day for 9-11 wks. They were then exposed to OZONE at 0.5 ppm fpr 140 min; and given intermittent exercise and tested for respiratory function, blood chemistry, and hematology. No interactive responses were observed; no changes due to combined stresses of O&lt;sub&gt;3&lt;/sub&gt; and Vit E. Vitamin E did not provide any protection in these studies against O&lt;sub&gt;3&lt;/sub&gt;.</td>
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This discusses methodology for studies which are reported in the citations noted below. They deal with human subjects exposed to lab simulations of smog pollutants and others, including OZONE, NITROGEN DIOXIDE, CARBON MONOXIDE, singly and in combination, in short 2 hr and 4 hr exposures. SULFUR DIOXIDE is also included. The exposure chamber conditions discussed include the concentrations of the stressors used, chamber temperature conditions (from 150°F-130°F), and compares these with Los Angeles extreme ambient conditions. The specific clinical, biochemical, and behavioral evaluations which are done are also discussed.

Other parts of this study will be found in this journal volume on pp 379-384 and 385-390.
**Title:** Experimental Studies on Human Health Effects of Air Pollutants. 2. Four-Hour Exposure to Ozone Alone and in Combination with other Pollutant Gases

**Authors:** Hackney JD, Linn WS, Mohler JG, Pedersen EE, Breisacher P, Russo A

**Performing Organization:** Rancho Los Amigos Hosp, Envir Hlth Labs, Downey CA.

**Publication:** Arch Environ Hlth 1975 (Aug);30:379-384

**Excerpt:**

In laboratory studies human subjects (4M healthy, 4M with history of allergy from exposure to air pollutants-sensitive group) were exposed to: OZONE, at 0.5 ppm; also NITROGEN DIOXIDE at 0.3 ppm; also CARBON MONOXIDE at 30 ppm. Exposures were to separate agents, or to combinations with ozone preceding NO2 or CO, given by inhalation 5 days/wk in 4 hour exposures, for 3 wks. Chambers were kept at 31°C and 35% RH. Treatments were week 1: O3 at 0.5 ppm; week 2: O3 at 0.5 + NO2 at 0.3; week 3: O3 at 0.5 ppm + NO2 at 0.3 ppm + CO at 30 ppm. In the sensitive group, at 0.5 ppm O3 there was reduced forced-vital-capacity (FVC) and increased airway resistance. There is shown a broad sensitivity to O3 if there is pre-existing airway hyperreactivity. There was no drop in function in healthy controls at O3 0.5 ppm alone or with NO2 at 0.3 ppm.

**Keywords:** ozone, nitrogen dioxide, carbon monoxide, combined stresses, pulmonary function, allergic sensitivity, interactive responses

**Notes:** Other parts of this study will be found in this same journal volume on pp 373-378, and 385-390
### Experimental Studies on Human Health Effects of Air Pollutants

**3. Two-Hour Exposure to Ozone Alone and in Combination with other Pollutant Gases**

**7. Author(s)**

Hackney JD, Linn WS, Law DC, Karuza SK, Greenberg H, Buckley RD, Pedersen EE

**9. Performing Organization Name and Address**

Rancho Los Amigos Hosp, Envir Hlth Labs, Downey CA

**16. Extract**

In laboratory studies human subjects (13M ages 22-41 yrs) were exposed to: OZONE at 0.5 ppm for 1 wk; or in a 3 wk experiment, on wk 1 to O₃ at 0.25 ppm, on wk 2 to O₃ at 0.25 ppm + NO₂ at 0.30 ppm, on wk 3 to O₃ at 0.25 ppm + NO₂ at 0.3 ppm + CO at 30 ppm; in another group, exposure was to O₃ at 0.37 ppm for 1 wk.

Normal healthy subjects and those sensitive, reactive allergically to pollutant exposures, were stressed as above and also in some studies exposed to heat, intermittent exercise. Exposures to O₃ at 0.5 ppm dropped forced vital capacity, forced expiratory vol, and respiratory flow rates. O₃ .25ppm caused no real changes, even with NO₂ 0.3 ppm and CO 30 ppm together. O₃ at .37ppm causes small drop in lung functions, more substantial at 0.5 ppm. Reactive subjects showed drop in FVC and FEV on successive days.

**19. Keywords**

ozone, nitrogen dioxide, carbon monoxide, combined stresses, pulmonary function, allergic sensitivity, interactive responses

**20. Notes**

Other parts of this study will be found in this same journal volume on pp 373-378, and 379-384
In laboratory studies rats were exposed to ALPHA-TOCOPHEROL at 10.5, 45, 150, 315 mg/kg of body wt; also OZONE at 0.7-16 ppm or NITROGEN DIOXIDE at 20-25 ppm. In the treatments with single and combined stressors, various diets with A-T deficiency or A-T added, or DL-methionine, or BHT added, were given for 4 wks before ozone or NO₂. A-T protects against lipid peroxidation in lung as a reciprocal function of the log of dietary A-T. A-T extends survival of rats exposed to toxic levels of O₃ and NO₂. Highest survival rates are at highest A-T, (also shown with ascorbic acid and methionine. At O₃ 0.6 ppm 4 hrs (LC₅₀) A-T prolongs life. At O₃ 0.8 ppm (like Los Angeles smog) continuous exposure is lethal, not altered by A-T. Lung lipid peroxidation provides the best measure of survival capability.

**Key Words**: alpha-tocopherol, ozone, nitrogen dioxide, combined stresses, alkane metabolism, lipid peroxidation, smog, antioxidants, interactive responses
**Extract**

In laboratory experiments rats (M, SD, age 21 days) were prepared with several diets (Group 1 fed a Vitamin E deficient diet; Group 2 fed V-E at 11 IU/kg in diet; and Group 3 fed V-E at 40 IU in diet. Feeding is halted 18-22 hr before breathing samples are collected. They are exposed in one variant to 8 wks of a V-E deficient diet, with supplemental V-E of 0, 11, 40 IU; then exposed to OZONE at 1 ppm for 60 min, and pentane and ethane measured in expired air. After O₃ exposure, pentane increases only in V-E deficiency.

**Key Words**

vitamin E, ozone, combined stresses, pentane, ethane, alkane metabolism, lipid peroxidation, lipid peroxidation, interactive responses
In laboratory studies human subjects (5M, 5F, ages 20-28 yr) were exposed to: OZONE at 0.3 ppm; EXERCISE to reach & hold 50% VO$_2$max for 1 hr; and ALPHA-TOCOPHEROL at 1200 IU in diet daily for 2 wk. Exercise alone induced lipid peroxidation and expired pentane rise. O$_3$ at 0.3 ppm does not change pentane out, beyond the exercise yield. C$_3$ at 1.0 ppm increases pentane only if there is an A-T deficiency. After A-T is replaced, pentane output goes down.
Irradiation of eg air in these plants creates OZONE, NITROGEN DIOXIDE, NITRIC OXIDE, NITROUS OXIDE, NITROGEN PENTOXIDE, etc. O₃ may be the most toxic of these in the internal environment of the facility. The report discusses present accepted limits for O₃ exposure; discusses some quantitative aspects of O₃ production, shows calculation of conc buildup, and states some ventilation requirements. All of these assume a ⁶⁰Co source in the plant.
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In laboratory studies rabbits (160 albino) were exposed to: HYDROGEN CYANIDE, range 0.28-0.94 ppm (av 0.5 ppm); CARBON MONOXIDE, range 170-580 ppm (av 200 ppm); NITRIC OXIDE, range 2.5-5.3 ppm (av 5 ppm); and NITROGEN DIOXIDE, range 0.04-0.1 ppm. These are gaseous constituents of tobacco smoke, eg smoking 3-6 hr exposes to 0.5 ppm HCN. Study showed that: HCN alone, 0.5 ppm for 1 or 4 wks; or HCN (0.5) + CO (200) for 1 or 4 wks; or HCN (0.5) + CO (200) + NO (5) for 2 wks had no effect on the morphology of the aortal intimal vasculature, or coronary arteries, or pulmonary arteries. NO at 5 ppm for 2 wks caused minor changes in morphology of lungs, endothelium of pulmonary and coronary arteries, and aorta.
Effect of Exposure to 43 PPM Nitric Oxide and 3.6 PPM Nitrogen Dioxide on Rabbit Lung

In laboratory studies rabbits (12 M) were exposed to NITRIC OXIDE at 43 ppm; also NITROGEN DIOXIDE at 3.6 ppm in air for 6 days. No changes in pulmonary morphology or lung function were seen. The report discusses species differences in responses and greater susceptibilities of smaller rodents to air pollutant toxins.

nitric oxide, nitrogen dioxide, combined stresses, toxicity, pulmonary function, smoking, interactive responses
In laboratory studies, rats (albino) were exposed to: AMMONIA, at 3 and 6 mg/M³; also NITROGEN DIOXIDE, at 0.5 and 1.5 mg/M³ (each conc was about 30% of the max permissible conc in human worker zones). These were given separately or together by inhalation 7 hr/day, 5 x/wk, for 4 mo. At some point after exposures, Staphylococcus, human pathogen strain was given intranasally. Observations were made of the CNS, olfactory threshold, blood chemistry, lung morphology and function, and development of respiratory infection. NO₂ induced more pronounced changes than NH₃. NH₃ (6 mg/M³) + NO₂ (1.5 mg/M³) enhanced the development of respiratory infection. Also either alone or both at these conc cause more severe pathological changes in rat lungs which had sustained repeated respiratory microbial infections.

**Key Words:** ammonia, nitrogen dioxide, infection, combined stresses, pulmonary function, interactive responses
Effect of Ferrous Sulfate Aerosols and Nitrogen Dioxide on Murine Pulmonary Defense

In laboratory studies mice were exposed to NITROGEN DIOXIDE at 1 ppm; also FERROUS SULFATE, aerosols (av diam 0.4 um) at 290 ug/M³, by inhalation for 24 or 48 hr, prior to or 4 hr after INFECTION with Staphylococcus aureus or Streptococcus Grp 3 by inhalation. NO₂ and/or FeSO₄ 24 or 48 hr exposures do not impair lung inactivation of Staph aureus. NO₂ and/or FeSO₄ 24 or 48 hr exposures decrease inactivation of inhaled Strep Grp C, and reduced survival times, without changing mortality. Exposure to either for 48 hrs prior to infection increases proliferation of the Strep C. FeSO₄ and NO₂ may interfere with defense mechanisms other than alveolar macrophage, especially the new influxes of phagocytes.

nitrogen dioxide, ferrous sulfate, infection, combined stresses, pulmonary pathology, interactive responses
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<td>Effects of Nicotine and Carbon Monoxide on Tissue and Systemic Changes in Rats</td>
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<td>Environ Res 1979 (June);19:202-212</td>
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<td>In laboratory studies rats (M SD) were exposed to: CARBON MONOXIDE at 100, 250,500 ppm; also NICOTINE TARTRATE at 0.5-1.0 mg/Kg IP 1x/hr for 4 hrs. Tests included: blood levels of COHb, glucose, lactic acid, SGOT, SGPT respiratory rate, core temperature, etc. Nicotine alone increases respiratory rate, core T, COHb, without enzyme change. Each alone make only small change in glucose, lactic acid. Nic + CO have synergistic interactions. Nic (1 mg/Kg) + CO(100-500 ppm) raises blood glucose, lactic acid, and plasma aspartate aminotransferase. Nic (1) + CO (500) also raises plasma alanine aminotransferase. Direct catecholamine actions are released by Nic.</td>
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<td>nicotine, carbon monoxide, combined stress, toxicity, plasma chemistry, interactive responses</td>
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In laboratory studies rats (M, Carworth) were exposed to: CARBON MONOXIDE (dose not avail) IP and into aortic-hepatic cannulae; also HYPOXIC HYPOXIA (levels not avail) to explore possible effects of CO on some sensitive metabolic enzymes. Greater drops in liver arterial O₂ content and venous O₂ tension are needed during CO exposure (compared with hypoxic hypoxia) to produce a given pharmacological response. With severe hypoxia drug metabolizing enzymes shift from blood flow limited (dependent) to O₂ limited systems. There are no data to show any direct effect of CO on such enzymes as Cytochrome P-450; its action is restricted to Hb bonding and related hypoxia.
In laboratory experiments mice (M) were exposed to: OZONE at 0.11-0.4 ppm; also NITROGEN DIOXIDE at 2.0-7.3 ppm; by inhalation singly or together. INFECTIOUS AGENT, 32P-labeled S.aureus in aerosol was instilled into lungs either 4 hrs prior to or after toxics exposure. Animals were prepared for analysis 10 min after last exposures. O3 over long periods (17 hrs) was the sole agent causing such ventilation problems as tracheobronchial irritation, increased airway resistance, and shallow breathing patterns. Combined exposure impaired bacterial defense; perhaps by oxidant damage to alveolar macrophages, a direct toxic action of O3 or NO2. Combined stressors did not affect physical removal of bacteria. O3 and NO2 act "indifferently" to cause this bacterial handling dysfunction at approx the individual gas injury thresholds.
In occupational survey in the chemical industries, workers (Group 1: healthy; Group 2: chronic ischemic heart disease; Group 3: chronic bronchitis or pneumonia) were exposed to AMMONIA, NITROGEN OXIDES, SULFUR DIOXIDE; SULFURIC ACID aerosols, in various mixes with total conc in air of working zones at av 15%-50% of max permissible conc. Measurements were made of olfactory thresholds, exercise capacity, and lung function. In general, olfactory thresholds rose and respiration and circulation efficiency dropped as function of toxics levels and presence of concurrent disease of the cardiovascular or respiratory systems.

sulfur dioxide, nitrogen oxides, sulfuric acid, ammonia, combined stresses, chemical industry, pulmonary pathology, heart disease, bronchitis, pneumonia, interactive responses
**Extract**

In laboratory studies human subjects (11M ages 23-38 yr) were exposed to: NITROGEN DIOXIDE at 5 ppm; also SULFUR DIOXIDE at 5 ppm; also OZONE at 0.1 ppm; by inhalation, alone or in combination, including ternary mixes. In some experiments, immediately after exposure, there was a bronchial challenge with acetylcholine aerosol at 1,2,3 %. In all of the NO₂ exposures, lung airway resistance and arterial O₂ transfer dropped. With combined stresses, 8/11 showed no greater effect than NO₂ alone, except in 3, where there was a recovery delay after increased airway resistance(M). NO₂+SO₂+O₃ mix had no further effect on PaO₂ or R. There was greater reactivity to Acetylcholine after exposure to the mix. It is necessary to reconsider present allowable levels, when mixes are involved.

**Keywords**

nitrogen dioxide, ozone, sulfur dioxide, combined stresses, acetylcholine, pulmonary function, interactive responses
**In laboratory experiments human subjects (8M ages 19-25, non-smokers, exercisers) were exposed to: SULFUR DIOXIDE at 0.37 ppm; also OZONE at 0.37 ppm, by inhalation, separately or mixed. **SO$_2$ alone showed no effect on max- and mid-expiratory flow in 2 hr, nor did the O$_3$ exposure. But SO$_2$ + O$_3$ showed an interactive effect: FEV (forced expiratory vol) dropped to 78% in 2 hr; mid-expiratory flow rate at 50% VC drops to 54%, peak expiratory flow rate to 79%, and vital capacity to 92%. SO$_2$ and O$_3$ interact rapidly on large wet lung interfaces, which become painted with H$_2$SO$_4$.**

**Key Words**

sulfur dioxide, ozone, combined stresses, toxicity, pulmonary function, interactive responses
In laboratory experiments, mice were exposed to NITROGEN DIOXIDE at 0.1 ppm, 24 hr/day, 7 d/wk for 1, 2, 3, 6 mo; also to OZONE at 0.1 ppm; exposures separately or in mixes, in some peak studies for 3 hr/day, 5 day/wk. At 1 hr after end of inhalation exposure, INFECTIOUS AGENT Streptococcus pyog. aerosol was instilled; in some animals there was re-exposure to the toxics for 14 days. Peak combined exposures did most to reduce resistance to Strep pneumonia and enhance mortality rates. 3-mo exposure reduced clearance of inhaled Strep, and dropped total cell count recovered in lavage and viability and phagocytic activity of alveolar macrophages. 1-2-mo exposure showed no big change in mortality or survival time. Sequence of exposures to toxic is important in reduced resistance to Strep pneumonia. Worst case is extended pollutant exposure even after Strep. Peaks are more stressful. Intermittent exposure standards are limited.
Health Effects of Short-Term Inhalation of Nitrogen Dioxide and Ozone Mixtures

In laboratory studies mice (F, CF-1 and CD2F1) were exposed to: NITROGEN DIOXIDE at 1.5-5.0 ppm; also OZONE at 0.05-0.5 ppm, each alone or in mixture, in single 2 hr exposure, or multiple 3 hr exposures daily 5 x/wk for 1, 2, or 4 wk, all by inhalation. At one hr after end of inhalation exposures, INFECTIOUS AGENT Streptococcus pyogenes Gp C was instilled into respiratory tract over 10 min period. Responses observed were mortality and lung bacterial clearance. There was a linear relation between mortality and conc of either NO$_2$ or O$_3$ alone. Survival times were shortened with 0.5 ppm O$_3$ or 3.5-5 ppm NO$_2$. NO$_2$ and O$_3$ showed an additive effect after single 2 hr exposure. With multiple exposures, there is an excess mortality. An apparent synergy comes from capacity to clear inhaled bacteria impaired by inhaled mix of toxics; not from changes in deposit sites.

Key Words: nitrogen dioxide, ozone, combined stresses, toxicity, infection, pulmonary pathology, interactive responses
**Title:** Pathology of Pulmonary Disease from Exposure to Interdependent Ambient Gases, Nitrogen Dioxide, and Ozone

**Authors:** Freeman G., Furiosi NJ, Mussenden R., Stephens RJ, Evans MJ

**Performing Organization:** Stanford Res Instit, Life Sci Div, Menlo Pk CA

**Publication:** Arch Environ Hlth 1974 (Oct);29:203-210

**Extract:**
In laboratory studies, rats (ages 1 mo) were exposed to: OZONE at 0.5 ppm and 0.9 ppm for 12, 24, 48, 144 hrs; also to NITROGEN DIOXIDE at 0.9 ppm on same schedule, in inhalation. Treatments were: O$_3$ alone at 0.5 or 0.9 ppm; NO$_2$ 0.9 ppm for 3 wks; O$_3$(0.9) and NO$_2$(0.9) continuously for 30 days; NO$_2$ at 2.5 and O$_3$ at 0.25 (10:1) for 24, 40, 96 hrs, and 2, 3, 26 wks. O$_3$ at 0.5-0.9 ppm in 24 hrs shows damage in bronchioles and alveolar ducts; NO$_2$ at 15-20 ppm changes epithelium of deeper bronchioles and ducts. There were additive effects of O$_3$(eg from smog) and NO$_2$ (eg from smoking found in chronic obstructive pulmonary disease), in related studies.

**Keywords:** ozone, nitrogen dioxide, combined stresses, smog, toxicity, pulmonary pathology, interactive responses
In laboratory experiments, guinea pigs (GP) and mice (M) were exposed to: OZONE at 0.34-1.35 ppm for 2 hrs; also NITROGEN DIOXIDE, at 5.2-13.0 ppm for 4 hrs, and effects compared. In GP, the earliest effects for O₃ or NO₂ were an increased respiratory frequency and decreased tidal volume; an irritant response, caused in each case by a different mechanism. These effects were found even after O₃ 2-hr exposure at 0.34 ppm. Previous exposure to O₃ provided no help in tolerance. In mice, the same activities were depressed.
### Evaluation of the Hazards of Ozone and Oxides of Nitrogen. Factors Modifying Toxicity

In laboratory experiments, rats, mice, and hamsters were exposed to: OZONE at 4-11 ppm (approx LD50) one time; also NITROGEN OXIDES (NO2, N2O5) at 0.2-500 ppm; each alone, or their mixes. NxoN did not modify O3 toxicity and mortality. O3 toxicity was enhanced by exertion, alcohol, respiratory infection, and in young animals. O3 toxicity was reduced or eliminated with intermittent exposure, and certain premedication.

#### Key Words
- ozone, nitrogen oxides, combined stresses, toxicity, infection, therapeutic drugs, prophylactic agents, interactive responses
**Title:** Studies of Ozone Toxicity. 1. Potentiating Effects of Exercise and Tolerance Development

**Authors:** Stokinger HE, Wagner WD, Wright PG

**Publication:** AMA Arch Ind Hlth 1956;14:158-160

**Abstract:** In laboratory experiments, rats and mice were exposed to: OZONE at 1 ppm for 6 hrs; alone or with EXERCISE in rotating cage 15 min/hr for 6 hrs; retested for tolerance after 1 day, then at 1, 2, 3, 4, 6 wks. There was enhanced toxicity to rats and mice from exercise during Ozone exposure. Ozone is fatal in 6 hrs av of exercise is done for 15 min/hr during each exposure. A marked tolerance to Ozone developed within 24 hrs, and persisted for 4-6 wks, allowing survival of normally lethal conditions, for a high tolerance group.

**Key Words:** ozone, exercise, combined stresses, adaptation, toxicity, interactive responses
In laboratory studies, human subjects (about 290 healthy adults) were exposed to: SULFUR DIOXIDE at 5 ppm; also SULFURIC ACID at 1 mg/M³; with one or both deposited via radiolabeled saline aerosol bolus as 3 um particles into large airways. Lung retention and clearance is faster when SO₂ + H₂SO₄ are present. Max expiratory flow rates fell greatly with SO₂, and less with H₂SO₄; the acceleration of clearance is an irritant response. This study at rest was followed by one with mixed aerosol or components, then exercise for over 50 min, then rest for 1.5 hrs. After 0.5 hr rest in healthy who had exercised, only the SO₂ appears to reduce expiratory flow rate (a response to irritant). No combined effects are shown.
In laboratory studies monkeys (170 cynomolgous M) and guinea pigs (400 GP) were exposed to: SULFUR DIOXIDE at 0.1-5.0 ppm; SULFURIC ACID at 0.1-1.0 mg/M³ as mist; FLY ASH (from coal) at 0.5 mg/M³, particle sizes of all avg 5 um. Treatments were single and mixes inhaled for 52 wk(M) and 78 wk (GP). SO₂ 5 ppm or ash 0.5 mg/M³ or their mixes caused no changes in lung histology, function, hematology or blood chemistry in M or GP. H₂SO₄ damage threshold was 0.1 mg/M³, significant over 1 mg/M³, with major impairment of lung ventilation and diffusion over 3.5 mg/M³. In ternary mixes, H₂SO₄ is the sole source of damage.

sulfur dioxide, sulfuric acid, fly ash, combined stresses, mist, pulmonary function, interactive responses
In laboratory studies, human subjects (3F, 5M, ages 12-14 yr, determined as "healthy" in tests with cytology, exercise, methacholine challenge, IgE, etc) were exposed to: SULFUR DIOXIDE at 1 ppm and/or SODIUM CHLORIDE (0.9 um droplet aerosol) at 1 mg/M^3, inhaled at ambient T of 220 C and 75% RH for 30 min, then EXERCISE on treadmill. Pulmonary function tests included total respiratory resistance, residual capacity, max flow, forced expiratory vol. At rest, SO₂ or NaCl alone had no or minor effects. SO₂ + NaCl caused small drop in forced expiratory volume. During exercise, NaCl alone had no effect; SO₂ or SO₂ + NaCl induced reductions in FEV and Vmax, with combined effects larger and longer. Effects found are lower than seen in asthmatic adolescents. The sites of deposition of stressor are more extensive after exercise.

**Title continued: "..Exposure to SO₂ Alone or SO₂ plus Sodium Chloride Droplet or Aerosol during Rest and Exercise"**

Other parts of this study will be found in Environ Res 1980; 22:145 and 1981; 25:340
In laboratory studies, human subjects (9 adolescents with history of extrinsic asthma, e.g., exercise-induced bronchospasm) were exposed to: sulfur dioxide at 1 ppm; also NaCl droplet aerosols (size 0.9 um) at 1 mg/mL, separately, or together, for 60 mins each. Lung function tests included: total respiratory resistance, max flow at 50% and 75% of expired vital capacity, forced expiratory volume, and functional residual capacity. Studies were made at rest alone. There were no significant changes caused by NaCl alone, but SO₂ + NaCl produced more significant decrease in pulmonary functions (at small airway sites) than either agent alone. Asthmatics were found to be more sensitive than healthy non-smoking adults.

**Keywords:** sulfur dioxide, sodium chloride aerosols, combined stresses, toxicity, pulmonary pathology, asthma, interactive responses
This discusses a number of method concepts, including the choice between preventive strategies, and estimation of anticipated case reductions after population exposure modification for one or more hazards. (This includes personal and community interventions). Estimates may be made without knowledge of the joint distribution of exposure to risk. General conditions may be stated so that the factor attributable risks, calculated by ignoring all other factors, are unbiased effect measures. Effect of a factor on an individual's disease risk is often described by "relative risk" (arithmetic change in disease ratios); for entire populations is used "attributable risk". For multifactor disease, RR uses multivariate techniques for unbiased estimates. The interest is in identifying risk factors rather than looking at population distributions, where data sources are limited. Examples are given for studies on alcohol, tobacco, oral cancer, and cholesterol, blood pressure and CV disease. Methods for reducing large variable pools to small arrays are here.

**Key Words:**
epidemiology, disease prevention, hazardous exposure, relative risk, attributable risk, multifactorial diseases, combined stresses, interactive responses, exposure models
In survey of methods for analyzing chronic disease outcomes, one matrix technic evaluating the contribution of 19 chemicals to the risk of liver angiosarcoma in vinyl chloride workers is discussed. There is a lack of good retrospective exposure data, so it is rare to determine a causal agent solely by using chronic disease occupational epidemiology. Early data may be on single agents, e.g., in uranium mining there are data on radium and radon but not on radon daughters, whose dose is 20x larger. Also, in some locales, the mines have been worked for Ag, Co, Bi, Ni, As, and exposure to these is possible. There is further discussion on gathering retrospective data, with examples in rubber workers, herbicide use, and also other multiple agent analyses in vinyl chloride workers, arsenic workers.

Keywords: Combined stresses, epidemiology, hazardous agents, occupational exposure, copper smelting, vinyl chloride, heavy metals, interactive responses, matrix method evaluation
**Epidemiological Investigation of Occupational Carcinogenesis using a Serially Additive Expected Dose Model**

**Authors:** Smith AH, Waxweiler RJ, Tyroler HA

**Performing Organization:**
- NEW ZEALAND: Wellington Clin Schl Med Dep Community Hlth
- USA: Univ NC SPH Occ Hlth Studies Gp, Raleigh

**Publication:**
Am J Epidemiol 1980 (6);112:787-797

**Extract:**
Studies of occupational carcinogens are complicated by: worker mobility within and between jobs and functions, and long latency between exposure and discovery of neoplasia. A Serially-Additive-Expected Dose Method shows cohort dose matrix, relating year 1st employed to age then, and to calendar year; facilitating study of relation of exposure dates and diagnosis or death dates. Also, a Cumulative Dose Concept, taken from work histories, further allows calculation of expected yearly exposure for each case. Data are needed on exposure to specific chemicals for each job in each yr. An example: angiosarcoma of liver and vinyl chloride exposure in a polymer plant is discussed. The methods can help to reveal the presence of combined factors, and whether they are acting independently or jointly.

**Keywords:** epidemiology, carcinogenesis, dose models, occupational hazards, combined stresses, caprylyl alcohol, vinyl chloride
Modes of survey may conceal the real occupational risks. Occupational factors are only one etiologic determinant in multifactorial diseases. Also, the diversity of industrial processes leads to a dispersion of risks, and it is hard to avoid sampling biases both for cases and for referent controls. Only after several surveys by several groups showing no risk for a certain factor can results be seen as valid. Cross-section surveys are easier to do than longitudinal. In chronic health impairments like degenerative diseases with multifactorial etiologies, the progress transition, some with long latency, from good health to impairments may be hard to detect in early phases. In the occupational setting not only must the direct and local industrial factors be considered, but the indirect atmospheric and other factors must be dealt with.
Anatomy of the Healthy Worker Effect - a Critique of Summary Statistics Employed in Occupational Epidemiology

Wen CP, Tsai SP

Univ Tex Schl Publ Hlth, Houston

Scand J Work Environ Hlth
1982 (Suppl 1);8:48-52

This is more accurately called the "active worker" effect and is expressed in lower morbidity and mortality referred to SMR (Standard Mortality Ratios). This may occur because of: improved economic status, subscription to medical insurance access and will to use care, changes in life style (eg socialization, reduced substance abuse, health education, reduced smoking, better mental health, etc) Although the SMR is all right for estimating relative risk in a small sample, there is a lack in comparability among SMRs (standards, age distributions, method issues, relative risk, life expectancy, length of observation, study methods. This may become exaggerated in cohort studies starting with young healthies but excluding retirees. It is recommended that at least three parameters be used to summarize mortality experience among the employed: relative risk, attributable risk, life expectancy.
EPIDEMIOLOGY

COMBINED STRESS EXTRACTS
In laboratory studies, guinea pigs were exposed to: MOTOR OIL dispersed as a submicron aerosol at 100 mg/m³ (The oil was either "new" Mobil SAE 10w-30 paraffin base with additives; or "used" from 3500 miles in engine of an old car.) SULFUR DIOXIDE, as a submicron aerosol was given at 1,10,50,100 ppm. Combined treatment typically used 50 ppm SO₂ + 100 mg/m³ oil as aerosol. Actual treatments: SO₂ alone; or SO₂ + motor oil simultaneously; or MO for 30 min then SO₂; or MO 1 hr, 18 hr gap, then SO₂ + MO, then SO₂ alone. Exposures were 1-1 hr. MO alone was an irritant; SO₂ increases pulmonary flow resistance. MO new and used protected against the SO₂ irritant response. Pretreatment with MO failed to protect against SO₂. The protective effect was lost when the MO was previously reacted with SO₂. The active ingredients appear to be detergents and dispersants in the MO.

sulfur dioxide, motor oil, combined stresses, pulmonary function, irritants, aerosols, interactive responses
In laboratory studies, guinea pigs were exposed (head only) to:

- **OIL** of one of three types: **MINERAL OIL** at 11 mg/m³ (Squibb medicinal, naphthenic, saturated HC), or **PARAFFIN OIL** at 14 mg/m³ (Baker lab gradem aliphatic straight and branched chain), or **LUBRICATING OIL** at 21 mg/m³ (ARCO light-lube, 67% paraffins, 32% naphthenic, 1% aromatic). They were also exposed to **SULFUR DIOXIDE** at 1, 10, 50, 100 ppm. Treatments were: O alone (aerosol av diam 0.5 μ); or **O** + dissolved SO₂; either for 1-1 hr. Paraffin Oil protects pulmonary function from SO₂ significantly at 1-10 ppm, completely at 50 ppm when given simultaneously. All the oils reduce response to SO₂ if they act at all; naphthenic oils at 100 mg/m³ failed to protect against SO₂ at 50 ppm. Oils were most effective in protection against irritant bronchoconstriction when given as 30 min exposure just before SO₂. Pulmonary flow resistance was the most sensitive measure of exposure to SO₂.

**Key Words:** sulfur dioxide, mineral oils, lubricating oil, combined stresses, pulmonary function, irritants, aerosols, interactive responses
In laboratory experiments, guinea pigs were exposed to: SULFUR DIOXIDE at 1 ppm; alone or in combination with SODIUM CHLORIDE aerosol at 1 mg/M³; also ambient atmosphere RELATIVE HUMIDITY at 40% RH or 80% RH. Treatments involved exposures for 60 min, recovery for 60 mins, and 2nd exposure for 60 mins, in 6 modes: SO₂ at low or high RH; NaCl aerosol at low or high RH; SO₂ + aerosol at low or high RH. Pulmonary flow resistance was measured. Lung compliance decreased during SO₂ + aerosol at high RH. There is a synergistic effect under these conditions. Deliquescent salts and high humidity result in droplets in which there is increased absorption of SO₂. Also acidity extends the effects of the NaCl aerosol itself.

**Key Words:**
- sulfur dioxide, sodium chloride aerosol, combined stresses, toxicity, pulmonary function, humidity, interactive responses
In laboratory experiments, guinea pigs (36) were exposed to:
SULFUR DIOXIDE at 1.1 ppm placed into SODIUM CHLORIDE aerosol
(NaCl at 1 mg/mL in water) particle diam 0.1-2.0 um. In the treat-
ments here exposure was to 1 mode for 1 hr, filtered air 1 hr, next
mode 1 hr, in random order: SO₂ in air under 40% RH; SO₂ in air
over 80% RH; NaCl in atmosphere under 40% RH; NaCl in air over
80% RH; SO₂ + NaCl at low RH; SO₂ + NaCl at high RH.
Pulmonary flow resistance increased significantly only when SO₂
and NaCl were given at high RH. Elevated RH enhances the inter-
action between SO₂ and certain aerosols. At high RH, the NaCl
particles hydrate and SO₂ uptake goes faster.

sulfur dioxide, sodium chloride aerosol, combined stresses,
toxicity, pulmonary function, humidity, interactive responses
In behalf of later epidemiological studies, a sample of the population was gathered at random from city directories, of adult population ages 25-74 yrs, in 6 communities following census format, to total of 18,000 candidates. The method for gathering data included: personal interview (and UK-MRC questionnaire), non-medical sampling of pulmonary function (eg with portable spirometer, of forced vital capacity, etc) and other assessment of health; air monitoring for SO₂, NO₂, O₃ and respirable particles (seeking gradations of exposure, eg to SO₂ to av 80 ug/M³. Smoking habits were noted. The validity of the approach and of the sample was verified for future data collection.
In a continuing epidemiological study in 6 communities where a population sample has been under observation, for one year there was monitoring continuously of total suspended particulates, respirable particulates, and the SO$_2$ and NO, NO$_2$ and O$_3$ fractions in these particulates and in the air. The monitoring was done outdoors and indoors, with spatial distribution measured at several sites where samplers were left. Some sources: smoking, fuel, cooking, heating were noted. Typically, in 6 outdoor sites, 4 were below 50% of NAAQS(Natl Atmo Air Qual Stds) limits, and 2 were violations.

**Key Words**
sulfur dioxide, nitrogen dioxide, combined stresses, toxicity, indoor environments, outdoor environments, pollutants monitoring, interactive responses
This review discusses: methodological problems in observational studies) eg measurement criteria, accuracy, use of secondary reports, controls; specific health effects of acute exposure to SULFUR OXIDES AND PARTICULATES, use of formal collections and reports of urban mortality and morbidity from U.S. and outside sources, with attention to CHESS (EPA Community Health and Environment Surveillance) data. A critique is provided on the epidemiological limitations of the current National Ambient Air Quality Standards. There are referrals to other work on identification of health effects, quantifying effects at different ambient concentrations, estimation of the number of people exposed, and the calculation of overall health risk associated with a given degree of "air quality".
In laboratory studies, human subjects (8, ages 14-18 yrs, with extrinsic asthma, eg exercise-induced bronchospasm) were exposed to SULFUR DIOXIDE at 1 ppm; also NaCl droplet aerosols, with particle size 0.9 um, at 1 mg/M³; given separately or together, then 30 min rest, then EXERCISE on treadmill for 10 min. Respiratory function tests included: total respiratory resistance, max flow at 50% and 75% expired vital capacity, forced expiratory vol, and functional reserve. Exercise concurrent with exposure to SO₂ + NaCl produced significant changes in the partial flow-volume curves, FEV 1.0, Vmax 50 & 75, and resistance. Changes were greater than those during exposure or at rest or seen in healthy subjects.
Among those models providing simplified extraction of real disease factors, additive models are not the only ones allowing adequate evaluation of the causal nature of several risk factors at a time. Some models may mask the interactions by arbitrary transformations used. Consider "attributable risk", which is used generally where there is a single binary risk factor, and assuming that causal effect of the factor is measured by an arithmetic difference in disease rates of exposed vs unexposed. "Population attributable Risk" requires data on "prevalence" of the factor. The relations among several epidemiological and statistical models are discussed.
**EXTRACT**

This discusses formulations of "no interaction" hypotheses applicable to case-control data, probability measures including procedures for analysis of multidimension contingency tables for factors measured at more than 2 levels. Comparison with existing epidemiological models of synergy are considered. Tests of null hypotheses for no-synergy are really tests of independence of a specific type in the risk factors under study.

**KEY WORDS**

epidemiology, interaction analyses, case-control studies, synergy indices, risk factors, multiple hazard exposures
ALTHERnatives to Rothman's Approach for Assessing Synergism (or Antagonism) in Cohort Studies

Hogan MD, Kupper LL, Most BM

NIEHS Biometry Br, Res Tri Pk NC; Univ NC SPH Dept Biostat, Chapel Hill

Am J Epidemiol 1978 (1);108:60-67

Rothman had proposed a ratio-type index for quantifying the joint effect of 2 or more factors acting in combination (eg binary variable like mortality) in the presence of non-zero background effects. Simple technics discussed here are: "linear contrast by observed risk"; an additive approximation to a probabilistic model of interaction; and a likelihood-ratio teat (an approximation variant on Rothman's model).

epidemiology, multiple risk factors, interaction analysis, statistical models, synergy
**REPORT DOCUMENTATION PAGE**

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<td>This methods paper discusses interaction, defined as a model-dependent concept, as in statistical models, including additive and multiplicative types. Synergy is discussed as a particular type of interaction, eg in public health models, based on a null model showing excess relative risk so that joint exposure to 2 or more factors yields more cases than exposure to the sum.</td>
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DD FORM 1 JAN 73 1473 (MOD.)
This methods paper discusses concepts for distinguishing interaction and synergism: the statistical, including additive models, with multiplicative models a special case of the additive model and where interactions are explicit and computable; biological, with many specific mechanism models; public health models (e.g., dealing with elimination of excess incidence rate due to a specific agent, by its removal from the scene.)

epidemiology, interaction analyses, additive models, multiplicative models, biological models, public health models, multiple risk factors
This discusses 2 agents as causes of an outcome, where either agent may modify the way the other produces the effect; the causal chains may have at least one common part. This also considers cause as linked to all-none effects, where other secondary factors at random may bring the system to readiness for all-none. Discusses linear dose-response curves, also synergies in non-linear responses eg where different % fractions of receptor populations need activation by agents 1 or 2, to produce response. Other ideas of synergy are discussed.

19. KEYWORDS
epidemiology, multiple exposure events, interaction analyses, additive models, synergy, antagonism
This report on epidemiological methods proposes use of specific yardsticks to examine possible synergies between 2 or more causes of disease. The interactions found may be "model dependent", and the approaches include:"statistical" interactions, interdependence between factors in a given model of risk, a predictive model not necessarily based on biological reality; "biological" interactions concerned with interdependence of several disease causing factors (eg initiation and promotion); specification of mechanism can be exact. Etiological factors may be additive, acting on the same step in a multistage process, or multiplicative, acting at different steps in the process."Public Health" interactions consider the proportional contribution of each risk factor to the number of disease cases occurring in a population;"decision making" interactions among classes of risk; eg risk is same for normo- and hypertensive CV complic from contraceptive, absolute risk is greater.

**Key Words**
epidemiology, multiple causative factors, statistical interactions, biological interactions, public health interactions, risk analysis, interaction models
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<th><strong>EXTRACT</strong></th>
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<td>This abstract of a presentation to the 13th meeting of the Society for Epidemiological Research discusses ways to determine if 2 or more risk factors are synergistic, considering that the identification of interaction is &quot;model dependent&quot;. Concepts include statistical interaction (defined arbitrarily), biological interaction (with specific causal mechanisms, which really sort out synergism vs independence), and public health interaction (where synergy denotes an excess over additivity of attributable incidences).</td>
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**KEY WORDS**

epidemiology, multiple risk factors, model-dependent interaction, statistical models, biological models, public health models, synergy, additive systems
SURVEYS

COMBINED STRESS EXTRACTS
Health Effects of Combined Exposures in the Work Environment

McDonald JC (Chf Ed) **

WHO (World Hlth Orgzn) Geneva, Switzerland

1981

76 P  272R


This excellent report covers these topics: types of combined exposures (CE); quantification of effects of CE; mechanisms of response to CE (interactions in environment, biological response to chemical agent CE, interaction of chemical and physical agents); review of relevant animal and human studies; personal factors affecting response to CE (genetic, disease, nutrition, treatment drugs, ethanol, smoking); CE and occupational cancer; epidemiological approaches; practical applications (in occ hlth practice, in standard setting, in research); and recommendations. Many studies are cited, but mechanisms of interaction are not discussed in detail.

** Chairman of Expert Committee which held Symposium on this topic, and of Board which prepared and Edited this report of the Symposium. Dr. McDonald is located at the London School of Hygiene and Tropical Medicine.
A number of topics on combined stresses (CS) are discussed: the characterization of interaction (type, order of occurrence, duration of exposure and severity); interaction of environmental stresses with host factors; specific stresses incl. electromagnetic, thermal, atmospheric, electromagnetic, chemical-toxic; host factors incl. genetic, age, sex, activity, fatigue, illness, nutrition, etc; complexity of simulation, and availability of simulators around the U.S. A variety of tables are presented.
**Title:** Strategy for the Assessment of Neurobehavioral Consequences of Environmental Factors

**Authors:** Tilson HA, Cabe PA

**Performing Organization:** NIEHS, Lab Behav & Neur Toxicol, Res Tri Pk NC

**Publication:** Environ Hlth Perspect 1978;26:287-299

**Extract:**
This discusses a proposal to validate behavioral tests with known neurotoxins and human toxicosis symptoms. Substances picked to test include: triethyl tin, acrylamide, methylmercury; and an array of psychomotor, cognitive, and affective response measures. There is extended discussion of specific neurological and psychological signs of deterioration; and utility of the procedures for arriving at prediction of events is considered.

**Key Words:**
chemical toxics, combined stresses, animal models, neurotoxins, human toxicosis, test strategy, neuropathology, behavior, interactive responses
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<td>Disabling Effects of Chronic Disease and Impairment. 2. Functional Capacity Limitations</td>
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<td>The vantage point here is the evaluation of functional limits as a primary consideration in obtaining Social Security disability support, and also affecting performance in the workplace. Topics discussed include: activity limitations data sources, prediction of severity of disability, adaptation and inherent capacity, changes in work activity and prediction of disability. Functiona; limit measures, social and demographic factors, and various consequence of functional limitations are also considered.</td>
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Mixed Exposures to Chemical Hazards

Freundt KJ

W GERMANY (FRG): Univ Heidelberg Fac Med at Mannheim, Dept Toxicol & Pharmacol

Occup Hlth Safety 1982 (8);6:10-42

Discussions of toxicodynamic interactions (eg at receptor sites) and toxicokinetic events (eg in transport, metabolism, transformation and disposal) are illustrated with examples of mixed toxics encountered in mines, foundries, steel working, auto repair etc. Metals (Cr, Ni, Cu, Fe, Mn, Ti, Pb, Zn), gases (mixed irritants: SO$_2$, O$_3$, NO$_2$) solvents encountered in work with shoes, furniture, fibers, handicrafts, painting); plastics chemicals, pesticides, dusts, and drugs in context of mixed exposure are considered in this analysis.

multiple chemical exposures, combined stresses, toxicity, pharmacokinetics, metals, gases, solvents, plastics, drugs, interactive responses
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Proc 9th Conf Envir Toxicol, Dayton, 1979, pp 58-71
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Cosmic Res (Kom Issledovann USSR) 1965 (2);3:256-258
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Human Fact 1972 (Apr);14:161-172

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Rept FAA-OAM-71-17, 1971; DTIC AD-729536

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NIH Grant 1981+ Gen Clin Res Ctr RR52-21, part 0001

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Neurosci Behav Rev 1979 (Winter);3:179-231

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(Inorganic and Methylmercury, Cadmium, Lead Metabolism,  
multiple factors to toxic vulnerability)  
NIH Grant, 1981+, NIEHS ES-P-1248

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APPENDIX B

SUPPLEMENTARY BIBLIO. 1
Kinds of basic problems discussed are: missing/deficient essential substance; deficiency or absence of enzyme system; alteration of cell transport of metabolite; abnormal antibody production; and abnormal proteins. For each selected topic is considered: the relative frequency of the disorder; specific environmental traits that can precipitate the abnormal response; tests for the lesion recommended for industry; and status of acceptance of industrial testing. Of 92 human disorders where a genetically determined eg enzyme deficiency has been identified, 5 were selected which meet certain prerequisites for improving effectiveness and reducing risk on the job. These are developed in detail: serum antitrypsin deficiency; glucose-6-pd; CS₂ hyperreactivity; abnormal antibody production; hemoglobins in sickle cell anemia.

19. KEY WORDS

    genetic lesions, toxic susceptibility, immunopathology, interactive responses
Nutrient-Toxicant Interactions: Susceptible Populations

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FDA Bur Foods Div Nutr Eash DC

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