# Environmental and Occupational Epidemiology / Exposure Assessment

- As Environmental Health (4) on 22 Oct. 2020
- Chapter 4 and Chapter 8 in the textbook 3rd Ed.
- Environmental and Occupational Epidemiology (Chapter 4 in 2nd Ed.)
- Key Concepts
  - Epidemiology: study of distribution and determinants of health and disease in human populations (incl. causal inference)
  - Environmental/Occupational epidemiology studies the role of exposures in the general environment/workplace by common methods
  - Epidemiological data complement other data (incl. toxicological data)
  - Optimal study design depends mainly on population's feature, exposure, and disease
  - Strength of conclusion is based on large sample size, accurate and precise measurement of exposure and disease
  - Avoiding bias (selection bias, information bias, and confounding) is important for valid causal inference
  - Necessary for risk assessment, determination of criteria/standard, policy-making

# An introduction to epidemiology

- Epidemiology pursues causal inference on exposure and disease: philosophical framework was given by Karl Popper's "Conjectures and Refutations" (Popper, 1963)
  - All hypotheses are tentative and may be disproved by further testing
  - A hypothesis has a greater scientific value when it has more possibility (test methods) of disproof
  - (ref.) Rothman KJ (2012) Epidemiology: An Introduction 2nd ed. Oxford Univ. Press – If you like to learn epidemiology, I recommend you to read this.
- Hill's checklist of causation (Hill, 1965)
  - Temporal relationship (absolutely required!): Exposure must precede disease
  - Consistency: The association is repeatedly observed in many studies
  - Large effect size: The exposed have much more disease than nonexposed
  - Positive dose-response: More exposure causes more disease
  - Biological plausibility: Some biological explanation makes it reasonable that A (exposure) causes B (disease)
  - etc.

# Types of epidemiological studies

- Descriptive studies
- Analytical studies for aggregated data
  - Ecological studies (correlation studies in group level) → making hypothesis
  - Meta-analysis → Assuming common tendency/mechanism for all population, generates strong evidence
- Analytical studies for individual level data
  - Clinical trials (typical intervention studies)
  - Observational studies
    - Natural experiments: eg. John Snow's comparison of cholera deaths between water-supply companies
    - Cohort studies: Comparison of disease occurrence between exposed cohort and nonexposed cohort, using Incidence Rate Ratios, Incidence Rate Differences, Risk Ratios, Risk Differences
    - Case-control studies: Comparison of past exposures between cases and controls, using Odds Ratios, special attention must be paid for recall bias
    - Cross-sectional studies: Studies of relationship between exposed status and disease status at same time data, using Odds Ratio

# Types of bias

- Selection bias: the relationship between exposure and disease in the study population doesn't represent that in general population
  - self-selection bias of the volunteer: eg. ethylene oxide -> breast cancer ?: if response was obtained from only 20% of the study population, the effect is overestimated
  - healthy worker effect
- Information bias
  - mismeasurement / misclassification: whether differential or nondifferential is important
  - recall bias
- Confounding: relating with both exposure and disease, and not the result of exposure
  - controllable by stratified analysis, restriction, and multivariate analysis

# Types of data analyses

- For category variables (esp. dichotomous variables)
  - Rate Ratios, Odds Ratios with confidence intervals: for relative levels of the effects
  - Rate Differences with confidence intervals: for absolute levels of the effects
  - Fisher's exact test - calculating p-values (probability of getting the actual data under the null-hypothesis of independence): strong effect of sample size should be paid attention
- For continuous variables
  - Typically regression analysis (for exposure and disease) or analysis of variance
    - linear regression model
    - logistic regression model
    - poisson regression model
    - multilevel model
    - One-way ANOVA
    - Multi-way ANOVA

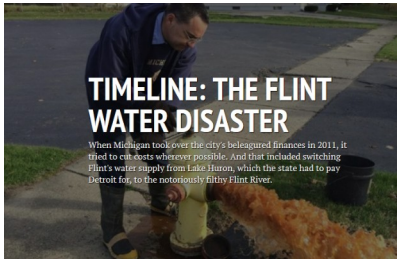
    etc.

# Environmental epidemiology

- Environmental agents, large number of people are exposed involuntarily (vs. individual voluntary exposure to tobacco, alcohol)
- Both possibility to cause epidemics and endemic diseases
  - Neuropathy outbreak in Madrid in 1981 <- oil contaminant
  - Gastrointestinal illness outbreak in Milwaukee in 1993 <- drinking water contamination by cryptosporidium
  - Endemic diseases are caused by constant, low level exposure
    - possible contribution of radon gas in homes to lung cancer
    - dioxin in the diet contributing to cancer rates
    - environmental lead exposure to children causes neurological deficits
  - Relationship between environmental agents and background levels of disease in developed countries is a kind of endemic diseases' study (becoming a large study focus, but difficult to detect such associations)

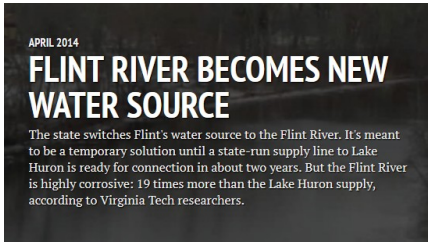
# Lead poisoning by polluted drinking water in Flint City, Michigan, USA

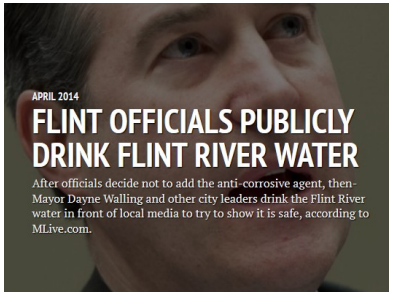
- Source:
  - http://pubs.acs.org/doi/ipdf/10.1021/acs.estlett.7b00226
  - https://www.pbs.org/newshour/science/study-confirms-lead-got-flints-water
  - http://edition.cnn.com/2016/03/04/us/flint-water-crisis-fast-facts/index.html
  - http://cdn.knightlab.com/libs/timeline3/latest/embed/index.html?source=1qlKcxYQhkjwsuCfQ5uQ0y7_GEQ3pNyGeCm5ooBqFhDA (see, below timeline)
  - https://www.epa.gov/flint
- Symptoms, cause and action:
  - Rashes in children, which may be caused by lead in drinking water
  - Lead contamination of drinking water came from old pipes, triggered by switching source water from Lake Huron to Flint River. This switch was due to poor financial situation of the city. After the finding of lead intoxication (2015), the use of Flint River water was stopped.
  - Flint residents now drink bottled mineral water instead of piped water, while the water quality is almost recovered in 2017.



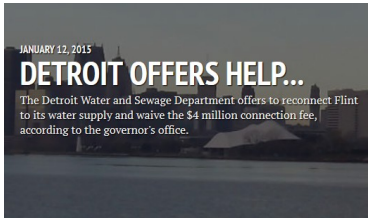






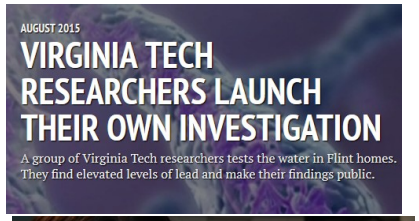



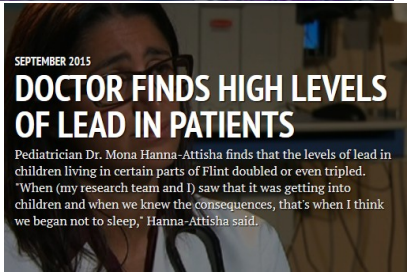










# Occupational epidemiology

- Illness or injury associated with workplace exposures
  - Stressful repetitive motion ~ carpal tunnel syndrome （手根管症候群 in Japanese）
  - Welding ~ lung cancer
  - Silica ~ kidney disease
  - Poor office ventilation ~ respiratory illness
- Relatively high level exposure to relatively small number of people, comparing with the target of environmental epidemiology
- Scientifically easy to study, but economically and politically controversial (often faces conflict of interest)
- Historically, occupational cancer was studied in relation to high level exposure to many kinds of occupational contaminants (asbestos, aniline dyes, silica, nickel, cadmium, arsenic, dioxin, beryllium, acid mists, radon gas, diesel fumes): It's already clear. Studies completed.
  - Much lower level environmental exposure has the same carcinogenicity? is still the target of the study (radon gas in homes, arsenic in water, asbestos are already clear, but dioxin's low level carcinogenicity is still unclear)
- Nowadays, subjects of occupational epidemiology involves issues more difficult to study (job stress ~ heart disease?, lifting ~ back strain?)

# Finding the occurrence of clusters

- In both environmental and occupational epidemiology, finding disease clusters is important
- Cluster: an apparently elevated number of disease cases in a limited area over a limited period, suggests common cause
  - Sometimes difficult to find: eg. 3 cases of childhood leukemia were found in the same street → unusual, but not found due to the ward of disease statistics being composed of a dozen streets
  - For rare diseases, statistical power is too small to detect the effect by cohort study, so that only case-control study is applicable to such situation
  - In most cases, researchers cannot find common cause from the cluster. (exceptions) Cluster of asthma in Barcelona in the early 1980s had common cause of soybean dust in the air.

# Measuring exposure

- Measuring exposure with sufficient accuracy is very important (see, next topic)
- Most difficult exposure assessment may occur in the retrospective case-control study (avoiding recall bias is difficult)
  - Constructing job-exposure matrix (JEM) → cross classification of jobs and exposure levels across time → Based on recent exposure data, researcher can extrapolate past exposure by jobs
  - Measuring the biomarker of exposure → alternative method to estimate past exposure
    - pesticide exposure ~ Parkinson's disease: organophosphate pesticide is rapidly metabolized, so that difficult to detect as biomarker, but organochlorine pesticide has longer biological half life and easy to detect. DDE is the principal metabolite of DDT, being still detected in serum of US population, though DDT use is already prohibited

# Occupational epidemiology example

- Based on National Death Index (in USA), death certificate to determine cause of death for 4626 workers in the cohort, exposed to different silica level
- Stratified analysis to control confounding by age, race, sex, calender time
- 109 workers were killed by lung cancer
- 23 workers were killed by end-stage kidney disease
- End-stage kidney disease and silicosis were strongly related with the exposure
- (Source: Table 3.1 of Frumkin's textbook 2nd Ed., pp.95)

| | Exposure levels (Figures are rate ratio to national general population, same age, actual numbers of death are shown with parenthesis) | | | |
|---|---|---|---|---|
| Cause | Q1 low | Q2 | Q3 | Q4 high |
| Lung cancer | 1.00 (17) | 0.78 (21) | 1.51 (20) | 1.57 (16) |
| End-stage kidney disease | 1.00 (2) | 3.09 (5) | 5.22 (6) | 7.79 (5) |
| Silicosis | 1.00 (1) | 1.22 (2) | 2.91 (4) | 7.39 (7) |

# Environmental epidemiology examples

- Air pollution (mostly sulfur dioxide excreted from petroleum complex since 1957) caused asthma outbreak in Yokkaichi city, Japan in 1960's (Kitagawa, 2012).
- Recreational water quality: the number of gastroenteritis outbreaks ~ exposure to recreational water -> increased 3-4 times from 1978 to 2004
- Haile and others (1999): gastrointestinal illness ~ swimming in marine waters incl. untreated runoff from storm drains in Santa Monica Bay?
  - Are there different risks of adverse health outcomes among subjects swimming at different distances from the storm drains?
  - Are risks of specific health outcomes associated with the concentration of specific bacterial indicators of water quality or with the presense of enteric viruses?
    - Adjusted RR for 400 yards away from drains: 1.2 for eye discharge, sore throat, HCGI (highly credible gastrointestinal illness), 2.3 for earache
    - Adjusted RR for within 50 yards from drains: 1.2 for cough, diarrhea, chills, 1.9~2.3 for eye discharge, vomiting, HCGI

# Epidemiology and risk assessment

- Past: Qualitative systematic literature review
- Today:
  - Quantitative **meta-analysis**: Weighted average of quantitative results (already published) across studies. (Originally used in clinical trials, but now used for observational studies too, it can combine different kinds of studies and measures.)
  - **Pooled analysis**: If **raw data** are available, this gives **a common exposure-response coefficients**.
  - Risk assessment: Determination of tolerable (acceptable) exposure level. Occupational exposure usually permit higher level than general public.

# Exposure assessment, industrial hygiene, and environmental management (Chapter 8)

- Key Concepts
  - Assessment of env. Exposure → Identify hazards → understand the effect of hazards on health → control the hazards → monitor
  - Industrial hygiene: anticipation, recognition, evaluation, control of workplace hazards
    - using air sampling, biomonitoring
    - hierarchical control: eg. substitution - ventilation - personal protection
  - Exposure science = new field: tools of industrial hygiene → general environment, leading to environmental management

# Exposure assessment

- Start from industrial hygiene (exposure at workplace)
- Know the hazard of exposures
  < Quantify hazardous exposures
  - eg. CO = asphyxiant (stop breathing)
    < How much CO exposure can be tolerated or dangerous? / How to measure, where and when they occur? → We can understand biological effect of CO exposure completely
  - In turn, we can identify acceptable level, set standard, monitor environments to be safe

# Four profession's paradigms of industrial hygiene

- Anticipation: Proactive estimation of health and safety concerns (commonly or potentially) related with a given occupational or environmental setting
- Recognition: Identification of potential and actual hazards in a workplace
- Evaluation: Visual or instrumental monitoring of a site, measuring exposures
- Control: Reduction of risk to health and safety through administrative or engineering measures

# Anticipation: Pre-preliminary assessment

- Traditional two focus areas: safety and health
- Safety hazards -> Needs safety engineering
  - Insufficient emergency egress (exit)
  - Slippery surfaces / risks of trips and falls
  - Chemical storage posing fire/explosion risk
  - Moving machinery
  - Unguarded catwalks
- Health hazards
  - Physical hazards: high noise levels, elevated temperatures and humidity, radiation, repetitive motion, ...
  - Chemical hazards
    - Acute: high level chlorine gas -> disability, death
    - Chronic: low level solvent exposure -> neurological damage / benzene -> bone marrow dysfunction, aplastic anemia / uranium -> lung cancer, ...
- New focus: environmental hazards (chlorine tank ruptures -> endangered safety, plume of organic wastes -> polluted drinking water, smokestack -> tree damage, ecological damage (reduced $O_2$ in water), land deterioration by heavy metals

# Recognition

- After anticipation of potential hazard -> Recognition of actual hazard
- By a site visit or walk-through (visual inspection of the facility)
  - both qualitative and quantitative info about occupational and environmental hazard
  - review job category, number of workers in each, job description, health/safety program
  - identify hazardous physical/chemical/biological exposures and mechanical/psychological factors
  - find subpopulations with different hazard levels

# Evaluation

- Where to sample?
  - area sampling: at a part of workplace
  - personal sampling: vicinity of individual workers
  - biological sampling: bodies of individual workers
- How to sample?
  - "representative of population" vs "worst case"
- Instruments
  - Direct reading instruments: eg. digital thermometer, hygrometer, noise monitor, Geiger counter, GC-on-a-tip for organic vapors, ...
  - Sample collection instruments: collect air sample on absorbing media (active vs passive sampling) -> measuring at laboratory
  - Biological monitoring: human hair, saliva, blood or urine are common to be used for exposure (nails for long-term exposure)

# Control

- Control = Primary prevention
- Approaches to modify workplaces (in Japanese, 作業環境管理)
  - Substitution: replacing hazardous material / process with a less hazardous one (eg. replace benzene by toluene)
  - Isolation: limiting access to the hazardous process (eg. place metal cage around moving parts to reduce the likelihood of clothes catching on the parts)
  - Ventilation: eg. introduction of fresh air, local exhaust ventilation, cool air
- Use protective devices
  - Fail-safe instruments: using two-buttons for operation
  - Personal protective equipments: gloves, safety glasses, ...
  - Administrative strategies: rotating workers to limit aggregation, ...(in Japanese, 作業管理)
- Example: Health hazard and control in painting https://www.youtube.com/watch?v=G4CE_dHBONs

# Exposure science


- Quantifying the contaminant exposures in daily activities
  - Magnitude, frequency and duration of exposure (exposure profile): the difference of peak and mean concentrations is important
  - Acute/chronic/subchronic exposures
  - Route and pathways of exposure: inhalation? ingestion? dermal?
  - Various methods
    - imputing or modeling (indirect exposure assessment, exposure scenarios, job-exposure matrix)
    - measuring environmental exposures (eg. environmental monitor NO2, PM)
    - measuring personal exposures (eg. air monitor during work: see photo above, source: http://www.cameco.com/uranium_101/mining-milling/more-topics/safety/)
    - aggregate and cumulative exposure assessment (cf. TDI / ADI)
    - measuring biomarkers (contaminants or its metabolic products in human body)
- Evaluating factors that influence exposures
- Exploring new measuring method: ingestion and skin absorptions are challenges. duplicate diet study, dietary diaries, and FFQ for ingestion, wearing skin patch for dermal exposure
- Exposure assessment ~ quantification of exposures in both occupational and environmental settings
- Example: Mercury exposure through fish consumption
  https://www.youtube.com/watch?v=MavZrSTDySY
  https://www.youtube.com/watch?v=lDRS0YUgqLw

# Example: Mercury exposure through fish consumption https://doi.org/10.1038/sj.jes.7500516

- Rees JR, et al. (2007) Toenail mercury and dietary fish consumption. *Journal of Exposure Science and Environmental Epidemiology*, 17: 25-30.

**Table 1.** Spearman correlations between [Hg] in toenails and dietary exposures.

| | r | P |
|---|---|---|
| *Method 1 (3-day fish consumption diary)* | | |
| Total fish consumption | 0.20 | 0.318 |
| *Method 2 (semiquantitative food frequency questionnaire (Willet et al., 1985)* | | |
| Combined fish and shellfish consumption | 0.48 | 0.012 |
| Omega fatty acids | 0.46 | 0.016 |
| Combined tuna and darkfish consumption | 0.43 | 0.027 |
| Total fish consumption | 0.41 | 0.035 |
| Shellfish consumption | 0.40 | 0.040 |
| Combined tuna and other fish (not darkfish) | 0.36 | 0.087 |
| Darkfish and other fish (not tuna) | 0.33 | 0.097 |
| "Other" fish consumption (not tuna, dark fish, or shellfish) | 0.26 | 0.184 |
| Dark fish consumption | 0.22 | 0.279 |
| Tuna consumption | 0.21 | 0.296 |
| *Method 3 (detailed fish consumption questionnaire)* | | |
| Weighted total fish consumption | 0.16 | 0.438 |
| Total fish consumption | 0.04 | 0.832 |

*Method 1. Water and seafood intake record*

*INSTRUCTIONS*: Please record your water and seafood intake for the 3 days before your interview.

| | 1 | 2 | 3 |
|---|---|---|---|
| Date | | | |

Record any seafood you ate. Specify the type of seafood, such as tunafish, shrimp, etc., and the number of portions you ate (1 portion = 4 oz.)

| Type of seafood | Portions | Portions | Portions |
|---|---|---|---|

*Method 2. Fish consumption questions from the semiquantitative food frequency questionnaire (Willett et al., 1985)*

The fish consumption questions are included within a large comprehensive dietary assessment. The possible responses are: Never, or less than once per month; 1 per mo.; 1 per week; 2–4 per week; 5–6 per week; 1 per day; 2–3 per day; 4–5 per day; 6+ per day.

*Please fill in your average use during the last year, of each specified food. Please try to average your seasonal use of foods over the entire year.*

*Canned tuna fish (3–4 oz.)*
*Dark meat fish, for example, mackerel, salmon, sardines, bluefish, swordfish (3–5 oz)*
*Other fish*
*Shrimp, lobster, scallops as a main dish*

*Method 3. Detailed fish consumption questionnaire. Have you eaten fish from a local pond, lake or river in the last year?*

1 Yes 2 No

IF YES, specify the type fish, typical amount consumed, frequency, and the name of the pond, lake, or river_____

If Subject reports eating "dark meat fish, for example, mackerel, salmon, etc." or "other fish" one or more times per month: *What types of fish do you eat? How often?*

| Type of fish | Never or less than once per month | 1–3 per mo. | 1 per week | 2–4 per week | 5–6 per week | 1 per day |
|---|---|---|---|---|---|---|
| Mackerel | | | | | | |
| Salmon | | | | | | |
| Sardines | | | | | | |
| Bluefish | | | | | | |
| Swordfish | | | | | | |
| Other:_____ | | | | | | |
| Other:_____ | | | | | | |
| Other:_____ | | | | | | |

If Subject reports eating "shrimp, lobster, scallops, etc. as a main dish" one or more times per month: *What types of shellfish do you eat? How often?*

| Type of fish | Never or less than once per month | 1–3 per month | 1 per week | 2–4 per week | 5–6 per week | 1 per day |
|---|---|---|---|---|---|---|
| Shrimp | | | | | | |
| Lobster | | | | | | |
| Scallops | | | | | | |
| Crab | | | | | | |
| Clams | | | | | | |
| Other: _____ | | | | | | |