HOUSE MEMORIAL 42: PARKINSON'S DISEASE AND PESTICIDE EXPOSURE

A Review of the Association between Pesticide Exposure and Parkinson's Disease

Heidi Krapfl, MS
Epidemiology and Response Division
New Mexico Department of Health

Presentation to the Legislative Health and Human Services Committee on November 7, 2013

Objectives

- 1) Obtain a review of historical pesticide use in New Mexico from the NM Department of Agriculture
- 2) Conduct a literature search of scientific studies on the relationship between pesticide exposure and Parkinson's disease (PD)
- 3) Prepare a report assessing the risk of pertinent populations of New Mexicans, given results of 1 and 2. Provide recommendations as appropriate.

Background and Definitions

- Signature Signs and Symptoms of PD:
  - Bradykinesia (slowness of movement),
  - Resting tremor (tremor that occurs when muscle is relaxed),
  - Cogwheel rigidity (increase in muscle tone causing resistance to externally imposed joint movements), and
  - Postural reflex impairment (automatic movements that control equilibration when the body is upright and moving)
- Pesticides:
  - Wide range of substances designated to deter or kill insects (insecticides), rodents (rodenticides), plants (herbicides), fungi (fungicides), etc.
  - Have subclasses based on their chemical components (e.g., organophosphate) or their application method (e.g., fumigant).

Background and Definitions

- In New Mexico, pesticides and pesticide applicators are regulated by the Pesticide Control Act, administered by the NMDA
- Rules promulgated under the Pesticide Control Act govern:
  - pesticide registration,
  - the licensing of pesticide applicators,
  - recordkeeping requirements,
  - standards for use, storage and disposal of pesticides,
  - penalties for noncompliance,
  - inspection of application equipment, and
  - applicator safety

Background and Definitions

- Epidemiology terms that will be used:
  - Odds ratio (OR): the odds of having a disease among those exposed versus those unexposed. If the odds are the same among those exposed and unexposed (OR=1), there is no increased risk
  - Positive association: authors found an increased risk (OR>1.0)
  - Confidence interval (CI): the margin of error associated with an estimate. If the CI includes one (1), the result is not considered statistically significant

Methods: Literature Search

- A systematic search for relevant information in the scientific literature via the search engine PubMed http://www.ncbi.nlm.nih/gov/sites/entrez?db=PubMed (July 2013).
- Key and free-text words included: "Parkinson's disease," "pesticide," "insecticide," "fungicide," and "rodenticide."
- Review included articles identified through PubMed and those submitted by the public group Pesticides and Parkinson's Committee (the deadline for the public to submit articles was August 2, 2013).

Methods: Inclusion and Exclusion Criteria

- Included:
  - Studies (whether through PubMed or submitted by the public) if:
    - Addressed PD among people
    - Also addressed pesticide exposure
  - Peer-reviewed journal articles, government agency reports, and reports from nationally or internationally recognized organizations and authorities in public health such as the World Health Organization (WHO)

Methods: Inclusion and Exclusion Criteria

- Excluded:
  - animal model (anything but human),
  - cell lines or cell cultures,
  - treatment/protective factors,
  - no measures of association (odds ratio, relative risk),
  - miscellaneous (no pesticide exposure or PD not addressed); mechanism of action study; biomarkers of exposure; case report (report of a single case of PD); predictive toxicity (extrapolation of animal toxicity data to predict human effects or extrapolation of toxicity based on chemical structure); letter to the editor; summary of conference), or
  - article written in language other than English.
  - review articles that summarized original articles that we have already included, except for those reviews that attempted to evaluate the level of evidence for the association between exposure to pesticides and PD development

Methods: Data Extraction and Synthesis

- Eight epidemiologists from NMDOH extracted data from the studies selected for review and recorded the information on a standardized "data extraction" form.
- Extracted data included information about study participants such as race/ethnicity, age, and sex, measure of association (odds ratio), statistically significant findings, and any recommendations the study made.
- Two of the epidemiologists working on the data extractions also conducted the data synthesis and analysis.
- Data from the extraction form were summarized into two main categories of PD articles:
  - pesticide exposure without genetic interactions and
  - pesticide exposure with genetic interactions.

Results: Studies

- Selection of Studies
  - PubMed Search Results: 1547 articles
  - 30 articles added from the PPC (submitted 94 article titles; of those 13 duplicates within the PPC list and 51 already included among the PubMed search results)
  - Total number of articles for review: 1577
    - Excluded 1473 articles, based on the inclusion/exclusion criteria (review of abstracts and/or full articles)
  - 104 studies included for full review/analysis

Results

- Categorization of Pesticides:
  - Chemical Class/Functional Type
    - General (specific pesticide not mentioned; includes functional categories such as herbicides, insecticides, fungicides)
    - Organochlorine,
    - Organophosphorus,
    - Botanical,
    - Quaternary ammonium, and
    - Carbamate or dithiocarbamate
- How Authors Inferred Exposure Occurred
  - Spraying pesticides,
  - Handling or direct contact,
  - Using or applying pesticides,
  - Performing jobs likely involving pesticide use, or
  - Unspecified exposure/use such as proximity to agricultural spraying

Results

- Exposure/Use Categories Identified:
  - exposure with pesticide use specified, including:
    - general use (occupational or residential use could not be distinguished),
    - agricultural use (including farming),
    - other occupational use, and
    - residential use (including gardening),
  - exposure with pesticide use not specified, including in:
    - agricultural setting,
    - another occupational setting,
    - proximity to a pesticide use area, and
    - residential setting.

Results: Pesticide Exposure without Genetic Interactions

- General Pesticides (61 studies):
  - 35 studies demonstrated statistically significant evidence of an association between pesticides and PD
    - Herbicides (7 studies), Insecticides (7 studies), Fungicides (2): statistically significant associations
  - 26 studies did not demonstrate a statistically significant association
- Organochlorine (12 studies):
  - Includes DDT, dieldrin, lindane
  - 7 studies demonstrated statistically significant evidence of an association between pesticides and PD
  - 5 studies did not demonstrate a statistically significant association

Results: Pesticide Exposure without Genetic Interactions

- Organophosphorus (8 studies):
  - Includes chlorpyrifos, parathion, malathion, diazinon
  - 3 studies demonstrated statistically significant evidence of an association between pesticides and PD (OR range=1.9-2.5)
  - 5 studies did not demonstrate a statistically significant association
- Botanicals (3 studies):
  - Includes pyrethrins, rotenone, neem (rotenone was only botanical pesticide examined)
  - All 3 studies demonstrated statistically significant evidence of an association between pesticides and PD (OR range=1.7-10.9)

Results: Pesticide Exposure without Genetic Interactions

- Quaternary Ammonium (8 studies):
  - Includes paraquat
  - 3 studies demonstrated statistically significant evidence of an association between pesticides and PD (OR range=1.36-3.01)
  - 5 studies did not demonstrate a statistically significant association
- Carbamate or Dithiocarbamate (4 studies):
  - Includes maneb, zineb, ziram
  - 2 studies demonstrated statistically significant evidence of an association between pesticides and PD (OR range=1.74-8.09)
  - 2 studies did not demonstrate a statistically significant association

Results: Reported Pesticide Uses

- General Use of Pesticides (26 results*):
  - Setting not specified (e.g. residential, agricultural, or occupational) or could not be separated
  - 17 results demonstrated statistically significant evidence of an association
  - 9 results did not demonstrate statistically significant association

*Some studies had multiple chemical classes. Each OR counted once per chemical class for a given study.

Results: Reported Pesticide Uses

- Agricultural Use (Including Farming) (14 results):
  - 6 results demonstrated statistically significant evidence of an association
  - 8 results did not demonstrate statistically significant association
- Other Occupational Use (16 results):
  - 9 results demonstrated statistically significant evidence of an association
  - 7 results did not demonstrate statistically significant association

Results: Reported Pesticide Uses

- Residential Use (Including Gardening) (6 results):
  - 3 results demonstrated statistically significant evidence of an association
  - 3 results did not demonstrate statistically significant association

Results: Reported Pesticide Uses

- Use Not Specified/Not Mentioned (25 results):
  - Includes agricultural setting (e.g., banana plantation workers), other occupational (e.g., clergy), proximity (e.g. residence downwind from farming), residence (e.g. past residency in fumigated house)
  - 9 results demonstrated statistically significant evidence of an association
  - 16 results did not demonstrate statistically significant association

Results: Pesticide Exposure with Genetic Interactions

- General Pesticides (11 studies):
  - 6 studies demonstrated statistically significant evidence of an association between pesticides and PD with genetic interactions (CYP2D6, MDR1, MnSOD, NQ01, and N0S1 SNPs) (OR range=3.17-4.9)
  - 5 studies did not demonstrate a statistically significant association between pesticides, PD, and genetic interactions
- Organochlorine (1 study):
  - 1 study demonstrated statistically significant evidence of an association between pesticides and PD, BUT gene (ABCB1) did not modify the risk

Results: Pesticide Exposure with Genetic Interactions

- Organophosphorus (2 studies):
  - Both studies demonstrated statistically significant evidence of an association between pesticides and PD with genetic interactions (PON1-55MM and PON1-192QQ) (OR range=1.95-5.30)
- Quaternary Ammonium (3 studies):
  - 2 studies demonstrated statistically significant evidence of an association between pesticides and PD with genetic interactions (DAT, GSTT1) (OR range=4.53-11.1)
  - 1 study did not demonstrate a statistically significant association between pesticides, PD, and genetic interactions

Results: Pesticide Exposure with Genetic Interactions

- Dithiocarbamate (1 study):
  - Study demonstrated statistically significant evidence of an association between pesticides (maneb and paraquat) and PD with genetic interactions (DAT)

Results: Historical Use of Pesticides

- New Mexico Department of Agriculture does not have data on use and amount of pesticides and where applied. This does not allow a determination of risk of pertinent populations
- Appendix I does outline selected pesticides by type, chemical class, registration status and if the given pesticide has been cancelled or is still being used

Conclusions

- Pesticide exposure without genetic interactions:
  - Majority of evidence suggested an association between PD and pesticide exposure, specifically:
    - herbicides and insecticides
    - organochlorine (lindane)
    - organophosphorus (chlorpyrifos)
    - quaternary ammonium (paraquat)
    - botanicals (rotenone)
    - mixture of dithiocarbamate (maneb) with paraquat

Conclusions

- Pesticide exposure without genetic interactions:
  - Other factors which were stronger predictors for PD than pesticides include:
    - family history of PD,
    - head trauma, and
    - lack of smoking

Conclusions

- Pesticide Use:
  - Good epidemiologic evidence for the association between the general pesticide use category and PD development
  - Inconclusive evidence for following specific uses:
    - agricultural use of pesticides, which included farming,
    - other occupational use, and
    - residential use of pesticides, which included gardening.
  - Inconsistent or inconclusive for use not specified category:
    - exposure with use not specified in agricultural, other occupational and residential settings as well as proximity to a pesticide use area.

Conclusions

- Pesticide exposure with genetic interactions:
  - Majority of evidence suggested that genes studied increased the risk of PD among pesticide-exposed individuals
  - These studies suggested that among those exposed to pesticides, certain genotypes may interact to increase the risk of PD

Recommendations

- No available data about specific pesticides historically used, amount, and where pesticides used to assess risk of pertinent populations in New Mexico
- However, following recommendations apply to anyone in New Mexico who uses pesticides

Recommendations

- 1) Individuals who decide to use pesticides should first protect themselves and others from exposure by following the directions for application that are appropriate for the given pesticide. Gardeners who want to reduce the amount of pesticides they use may wish to learn more about Integrated Pest Management (IPM) principles: http://aces.nmsu.edu/pubs/_circulars/cr-655/welcome.html.

Recommendations

- 2) Under the federal Worker Protection Standard, agricultural workers and pesticide handlers must be trained and informed about pesticides used on the establishment. Violations should be reported to NMDA.