Classification of Hazardous Drugs by NIOSH

Thomas H. Connor, PhD
Research Biologist
National Institute for Occupational Safety and Health

NIOSH Goals

- Protect workers from exposure to hazardous drugs
- Provide best possible guidance
- Generate hazardous drug list
- Avoid unnecessary drugs on list
- Include all hazardous drugs
- Update on a timely basis

U.S. Guidelines for Safe Handling of Hazardous Drugs

- ONS-1982: Chemotherapy
- OSHA-1986: Cytotoxic (Antineoplastic) Drugs
- ASHP-1990: Cytotoxic and Hazardous Drugs
- NIH-1992: Cytotoxic Drugs
- OSHA-1995: Hazardous Drugs
- NIH-2002: Cytotoxic Drugs
- NIOSH-2004: Antineoplastic and Other Hazardous Drugs
- ASHP-2006: Hazardous Drugs
ASHP Criteria for Hazardous Drugs

- Carcinogenicity
- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses

(American Society of Health-System Pharmacists, 1990)

NIOSH Criteria for Hazardous Drugs

- Any drug identified by at least one of the following six characteristics:
  - Carcinogenicity
NIOSH Criteria for Hazardous Drugs

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  - Teratogenicity or developmental toxicity
  - Reproductive toxicity in humans
  - Organ toxicity at low doses in humans (<10 mg/day) or animals (<1 mg/kg/day)
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  - Genotoxicity
  - New drugs that mimic existing hazardous drugs in structure or toxicity

(NIOSH, 2004)

“Low Doses”

- Not a fixed cut-off dose
- Used only for guidance
- "For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg/day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits of less than 10 µg/m³." 

(NIOSH, 2004)
Decision Making-Examples

- Often not clear-cut decision
  - FDA Reproductive Category X- Yes
  - FDA Reproductive Category D- Most times
  - Carcinogenic in humans- Yes
  - Indication of cancer in humans, animal data- Yes
  - Carcinogenic in one organ/strain animals- No
  - Positive Ames test- No
  - Positive in multiple in vivo genetox tests- Yes

Weight-of-Evidence

- Weight-of-evidence is the process by which multiple measurement endpoints are related to an assessment endpoint to evaluate whether significant risk of harm is posed to the environment.
  
  (Massachusetts Weight-of-Evidence Workgroup, 1995)

NIOSH Hazardous Drug List

- NIOSH evaluates each drug individually based on NIOSH hazardous drug definition
- Considerable variation within a class of drugs
NIOSH Hazardous Drug List

- Antineoplastic Agents-89
- Hormonal Agents-21
- Biological Agents-8
- Antiviral Agents-7
- Immunosuppressant Agents-5
- Antibiotics-1
- Vaccines-1

(NIOSH, 2004)

NIOSH Hazardous Drug List

- Original hazardous drug list (2004)
  - Utilized existing lists from 4 organizations
  - List generated by the Pharmaceutical Research and Manufacturers of America (PhRMA)

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  - NIH Clinical Center, Bethesda, MD (Revised 8/2002)
  - Johns Hopkins Hospital, Baltimore, MD (Revised 9/2002)
  - Northside Hospital, Atlanta, GA (Revised 8/2002)
  - University of Michigan Hospitals and Health Centers, Ann Arbor, MI (Revised 2/2003)
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Drug Classification

- American Hospital Formulary Service (AHFS)
  - Published by ASHP
  - Not all drugs listed

Antineoplastic Agents

- AHFS Classification 10:00
  - Alkylating Agents
  - Antibiotics
  - Antimetabolites
  - Topoisomerase II inhibitors
  - Hormonal Agents
  - Monoclonal Antibodies
  - Interferons
  - Vaccines
NIOSH Approach

- Review all new FDA drug approvals
- Review all new warnings on existing drugs
- Eliminate warnings that do not apply (sterility, etc.)
- Review Drug Package Inserts
- NIOSH internal committee
- Evaluate based on criteria in hazardous drug definition
- Separate into those that meet criteria and those that do not meet criteria
- Utilize external expert and stakeholder input

Black Box Warning (example)

ALKERAN®
(melphalan)
Tablets

**WARNING**
ALKERAN (melphalan) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe bone marrow suppression with resulting infection or bleeding may occur. Melphalan is leukemogenic in humans. Melphalan produces chromosomal aberrations in vitro and in vivo and, therefore, should be considered potentially mutagenic in humans.

Process to Update NIOSH Hazardous Drug List

NIOSH review of new drugs and warnings

- External review
- NIOSH review
- Public comment
- NIOSH review

Approval by Office of Director
Update to NIOSH Hazardous Drug List

- Recent update to hazardous drug list (2004-2007)
  - 70 Newly approved drugs
  - 61 Drugs with new warnings
  - 18 New additions by NIH
- Preliminary list for review
  - 82
- Revised list for review
  - 24 Additions, 1 Deletion (BGC)
- Final List
  - 23 Additions submitted to NIOSH Office of Director for approval

Other Issues

- Size of molecule
- Formulation
  - Solution for IV, IM, SC, topical administration
  - Tablet (coated/uncoated)
  - Capsule
  - Oral suspension

Molecular Weights

- Classical antineoplastic agents
  - 5-Fluorouracil 130
  - Cisplatin 300
  - Paclitaxel 854
Molecular Weights

- Classical antineoplastic agents
  - Cyclophosphamide 279
  - Carmustine 214

Molecular Weights

- Interferon
  - gamma 1b
    32,930 Daltons
  - alpha 2b
    19,271 Daltons

Molecular Weights

- Monoclonal antibodies
  - Rituxan
    143,860 Daltons
  - Herceptin
    145,332 Daltons
Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Molecular Weights 144-152 kDa</th>
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<tbody>
<tr>
<td>Gemtuzumab ozogamicin</td>
</tr>
<tr>
<td>Muromonab CD3</td>
</tr>
<tr>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>Pantumumab</td>
</tr>
<tr>
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<td>Ibritumomab tiuxentan</td>
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<tr>
<td>Trastuzumab</td>
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<tr>
<td>Infliximab</td>
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</tbody>
</table>

Monoclonal Antibodies

- Large molecular weights make uptake by oral, inhalation or dermal route unlikely
- Most are target-specific (should only bind to cellular receptor)

500 Dalton Rule for Skin Penetration

- Skin is a physicochemical barrier
- Small molecules can pass transcutaneously
- Compounds > 500 Daltons cannot be absorbed

(Bos and Meinardi, 2000)
Vaccine

- Bacillus Calmette-Guerin (BCG)
  - BCG preparation should be done using aseptic techniques
  - To avoid cross-contamination, parenteral drugs should not be prepared in areas where BCG has been prepared
  - A separate area for the preparation of BCG suspension is recommended
  - All equipment, supplies and receptacles in contact with BCG should be handled and disposed of as biohazardous
  - If preparation cannot be performed in a containment device, then respiratory protection, gloves and a gown should be worn to avoid inhalation or contact with BCG organisms

Tablets

- Coated-Not a concern unless crushed for certain populations
  - Pediatrics
  - Elderly
  - Patients unable to swallow tablets
- Uncoated-Dust
  - Crushed or not crushed
  - Inhalation
  - Dermal contact
  - Automated dispensing devices
  - Cross-contamination

Tablets

- Cyclophosphamide
  - 25 mg Coated Tablet
  - 25 mg Tablet
Film-coated Tablets

- Paxil
  - FDA Pregnancy Category D
  - Reports of >600 Cases of birth defects in offspring of patients receiving Paxil

Special Situation

- Oxytocin (Pitocin®, Syntocinon®)
  - Oxytocin stimulates contraction of uterine smooth muscle and is used to induce labor in pregnant women
  - Only women in late pregnancy are at risk from handling this drug

NIOSH Updates to List

- FDA is approving new drugs
- FDA is issuing new warnings on existing drugs
- More oral chemotherapy is being used for longer treatment times
- New drug formulations being developed
NIOSH Updates to List

- Second update is underway
- Plan to carry out on a regular basis. (every other year)

NIOSH Collaborators

- D. Gayle DeBord
- Barbara A. MacKenzie
- James D. O’Callaghan
- Douglas B. Trout