

Handling Hazardous Drugs Implementation Strategies for a Safer Work Environment

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Program Objectives

- Describe the documented risk associated with handling hazardous drugs (HDs)
- Compare the OSHA, NIOSH Alert, and the ASHP 2006 Guidelines on HDs
- Identify engineering controls and equipment used to minimize the risk of exposure of HDs
- Describe the potential impact of USP <797> on the handling of HDs
- Identify three current models for implementing a pharmaceutical HDs waste management program

Understanding the Personnel Risks Associated with Hazardous Drugs

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The findings and conclusions of this presentation have not been formally disseminated by NIOSH and should not be construed to represent any agency determination or policy.



Background Issues

As the number of cancer and other chronically ill patients increases, the use of drugs to treat these diseases will grow, resulting in a greater potential for exposure of the health care worker.



Background Issues

Other factors may contribute to increased exposure: use of antineoplastic drugs for non-cancer diseases, special procedures, veterinary oncology

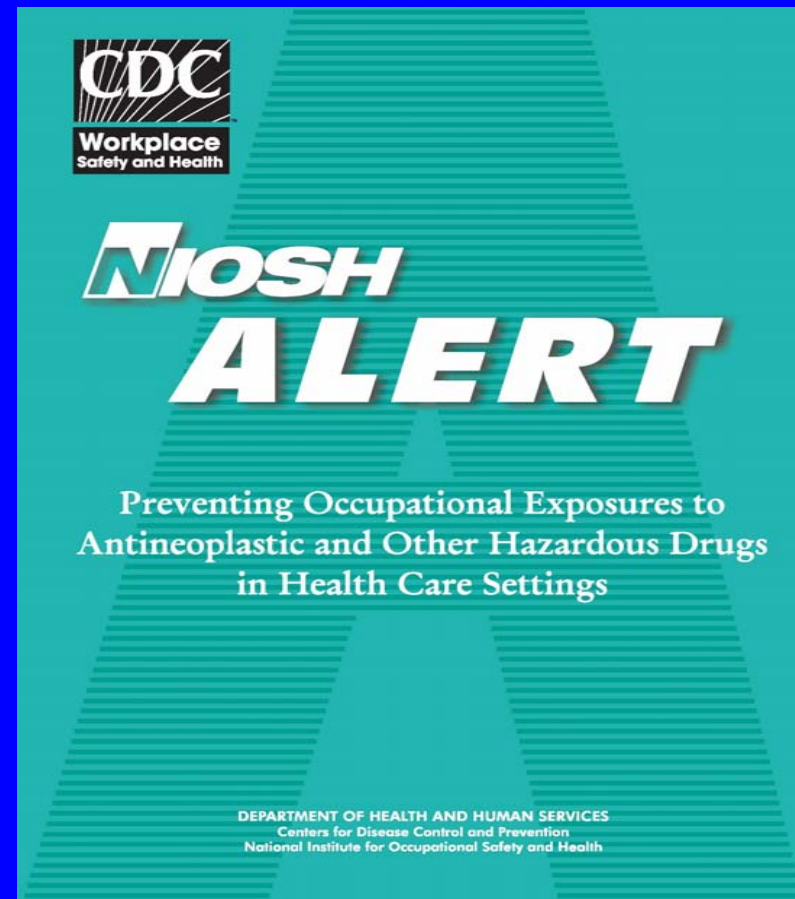


Definition of Hazardous Drugs

- **Carcinogenicity**
- **Teratogenicity or other developmental toxicity**
- **Reproductive toxicity**
- **Organ toxicity at low doses**
- **Genotoxicity**
- **Structure and toxicity profiles of new drugs that mimic existing hazardous drugs**
(NIOSH, 2004)

Composition of Hazardous Drugs

- Approximately 140 hazardous drugs identified (NIOSH, 2004)
- Two-thirds are antineoplastic drugs
- Remainder are: antivirals, immunosuppressants, monoclonal antibodies



Concerns about Hazardous Drugs

- **Acute toxicity**
- **Reproductive/developmental effects**
- **Cancer**
- **Genotoxicity**

Acute toxicity

- **Headache**
- **Allergic reactions**
- **Skin/mucous membrane irritation**

Pregnancy Category D or X Antineoplastic Drugs

FDA Category	No. Agents	Definition
D	46	There is clear evidence of risk to the human fetus, but the benefits may outweigh the risk for pregnant women.
X	5	There is clear evidence that the medication causes abnormalities in the fetus. The risks outweigh any potential benefits for women who are pregnant.

Reproductive Outcomes (health care workers)

Endpoint	No. Pos/Total	No. Significant
Spontaneous Abortions	4/5	2
Congenital malformations	3/4	2
Stillbirths	2/2	0

(Dranitsaris et al, 2005)

Carcinogenicity of Antineoplastic Drugs

IARC Group	No. Agents	Definition
1	11 + 2 combinations	Known Human Carcinogen
2A	12	Probable Human Carcinogen
2B	11	Possible Human Carcinogen

Carcinogenicity of Antineoplastic Drugs (health care workers)

- **There is some limited evidence for cancer in health care workers exposed to antineoplastic drugs (Skov et al.1990; Skov et al.1992)**
- **No recent studies**
- **No studies in U.S.**

Genotoxicity of Antineoplastic Drugs

- Antineoplastic drugs are **genotoxic** in:
 - Laboratory studies (in vitro and in vivo)
 - Treated patients
 - Health care workers

Known Hazards of Antineoplastic Drugs

Carcinogenicity	34 + 2 Combo: Group 1, 2A or 2B
Teratogenicity	51: Category D or X
Reproductive	Many
Organ toxicity	100% at high doses
Genotoxicity	Majority: animals and humans

Commonly Sampled Drugs

- Drugs are used as “marker” drugs
- Cyclophosphamide, ifosfamide, fluorouracil, methotrexate, doxorubicin, platinum-containing compounds

Sampling Strategies

- **Surface wipe samples**
- **Area air samples**
- **Personal air samples**
- **Drug vial samples**
- **Patch testing**
- **Urine testing**



Analytical Procedures

- **HPLC-UV**
- **LC-MS-MS**
- **GC-MS (GC-MS-MS)**
- **Voltammetry (platinum)**
- **IPC-MS (platinum)**

Surface Contamination Studies

- **27 Published studies**
- **All studies detected measurable levels of at least one drug**
- **Contaminated areas included: biological safety cabinets, floors, counters, IV bags, keyboards, gloves, transport containers, patient tables, chairs, waste containers**

Surface Contamination Studies

- In the early 1990s, several studies were carried out by Sessink in the Netherlands and one by McDiarmid in the U.S.
- Documented contamination of the work environment with antineoplastic drugs

Surface Contamination Studies

- In 1999, Connor et al. demonstrated surface contamination with cyclophosphamide, ifosfamide and fluorouracil in pharmacy and patient treatment areas in three hospitals in the U.S. and three in Canada

Surface Contamination Studies

- **75 % of pharmacy and 65 % of patient treatment areas were contaminated with at least one of the three drugs**
- **Drugs were detected in adjacent areas where drugs were not handled**

(Connor et al, 1999)

Air Sampling Studies

- **16 Published studies**
- **Particulate collection on paper or glass filters**
- **Low percentage of samples contained drugs**
- **Drug levels were usually low**

Air Sampling Study in UK

Drug	Area ng/M ³	Personal ng/M ³
Platinum	0-0.21	<LOD-5.3
Cyclophosphamide	0-4.8	<LOD-57
Ifosfamide	0-2.2	<LOD-2763
Methotrexate	<LOD	<LOD-215

(Mason et al, 2005) (LOD=limit of detection)

Sampling Drug Vials

- **11 Published studies**
- **Many drugs, lot numbers and manufacturers examined**
- **Drug vial exteriors are often contaminated with the drug they contain**
- **Some vials reach several 100 μg per vial**
- **Not always the result of damage during shipping and handling**

Sampling Drug Vials

- A recent report by Connor et al (2005) documented external contamination of drug vials in the U.S. from several manufacturers and lot numbers
- Vials were sampled at the NIH Clinical Center Pharmacy and VA Medical Center Pharmacy

Sampling Drug Vials

- 100 % of cyclophosphamide vials at NIH and 89 % at VA were contaminated
- Ifosfamide contamination varied with manufacturer
- 7 % of fluorouracil vials were contaminated, but some had high levels of contamination
(Connor et al, 2005)

Patch Testing

- **Minoia et al (1998) examined patches placed on workers**
- **Over and under the gowns**
- **Sampled for cyclophosphamide and ifosfamide**
- **Many patches were contaminated with one or both drugs**

Urine Testing

- **18 Published studies**
- **All but two reported detectable levels drugs in the urine**
- **In four studies, drugs were found in the urine of workers with no apparent direct contact with the drugs**

Urine Testing

- Pethran et al (2003) measured several drugs in the urine of 100 German health care workers
- 40 % of the workers had cyclophosphamide in their urine
- Despite use of BSCs and PPE, workers were still exposed

Biological Testing

- **Urine Mutagenicity**
- **Chromosomal Aberrations**
- **Micronuclei Induction**
- **DNA Damage**

Biological Testing

- **>150 Published Studies**
- **~ 50% reported a significant finding**
- **Many more than expected by chance**
- **Something must be driving the outcomes**
- **Exposure to antineoplastic drugs is the common factor**

Biological Testing

- **Chromosomal aberrations significantly different from control populations**
- **Chromosomal aberrations are significantly associated with cancer later in life**

(Bonassi et al, 2004)

Evidence for a Health Concern

- **Most, if not all, workplaces are contaminated**
- **Exposure documented by drugs in the urine of health care workers**
- **Genotoxicity documented by several biological markers**
- **Reported reproductive effects in workers**
- **Some evidence of cancer in workers**

Conclusions

- **Surfaces in all pharmacy and patient treatment areas should be considered to be contaminated with the drugs that are used in these areas.**
- **While some airborne levels of drugs are present, they are not likely to significantly contribute to exposure.**

Conclusions

- **The exterior of drug vials should be considered to be contaminated with vial contents.**
- **Health care workers may have measurable levels of hazardous drugs in their urine, even if not in direct contact with them.**

Conclusions

- **Since only a small fraction of hazardous drugs have been examined, it may be assumed that the workplace is also contaminated with other drugs.**

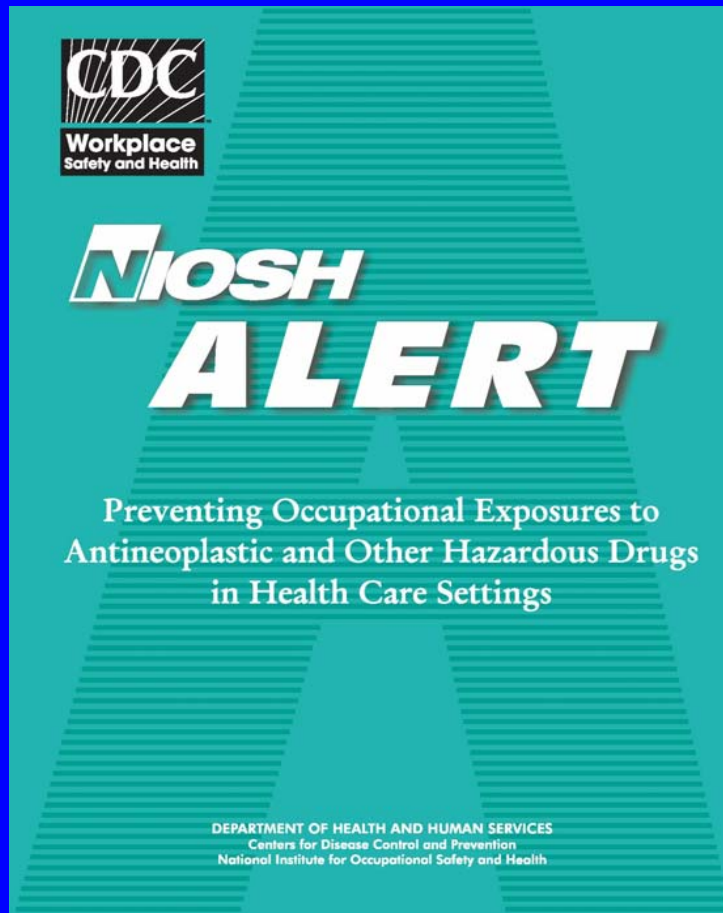
Conclusions

- **Biological monitoring studies indicate a possible increased risk of cancer in health care workers who have increased levels of chromosomal aberrations.**

Conclusions

- **Because of the ubiquitous nature of contamination with hazardous drugs**
 - **proper engineering controls**
 - **administrative controls**
 - **personal protective equipment****should be in place at all times where hazardous drugs are handled.**

Additional Information



<http://www.cdc.gov/niosh/docs/2004-165/>

Tear-out sheets and list of hazardous drugs available in Spanish (website and print versions)

List of hazardous drugs is currently being updated