A healthcare worker is shown from the back, wearing a blue protective gown and a white hairnet. They are working inside a biosafety cabinet, using a pipette to transfer liquid from a vial. The cabinet's interior is illuminated by a yellowish light, and various pieces of equipment and a hanging bag are visible in the background.

*Chromosome 5 and 7 Abnormalities in
Healthcare Workers Handling
Anti-Neoplastic Drugs*

Melissa A. McDiarmid, MD, MPH, DABT

Mechanism of Action of Selected Classes of Antineoplastic Agents

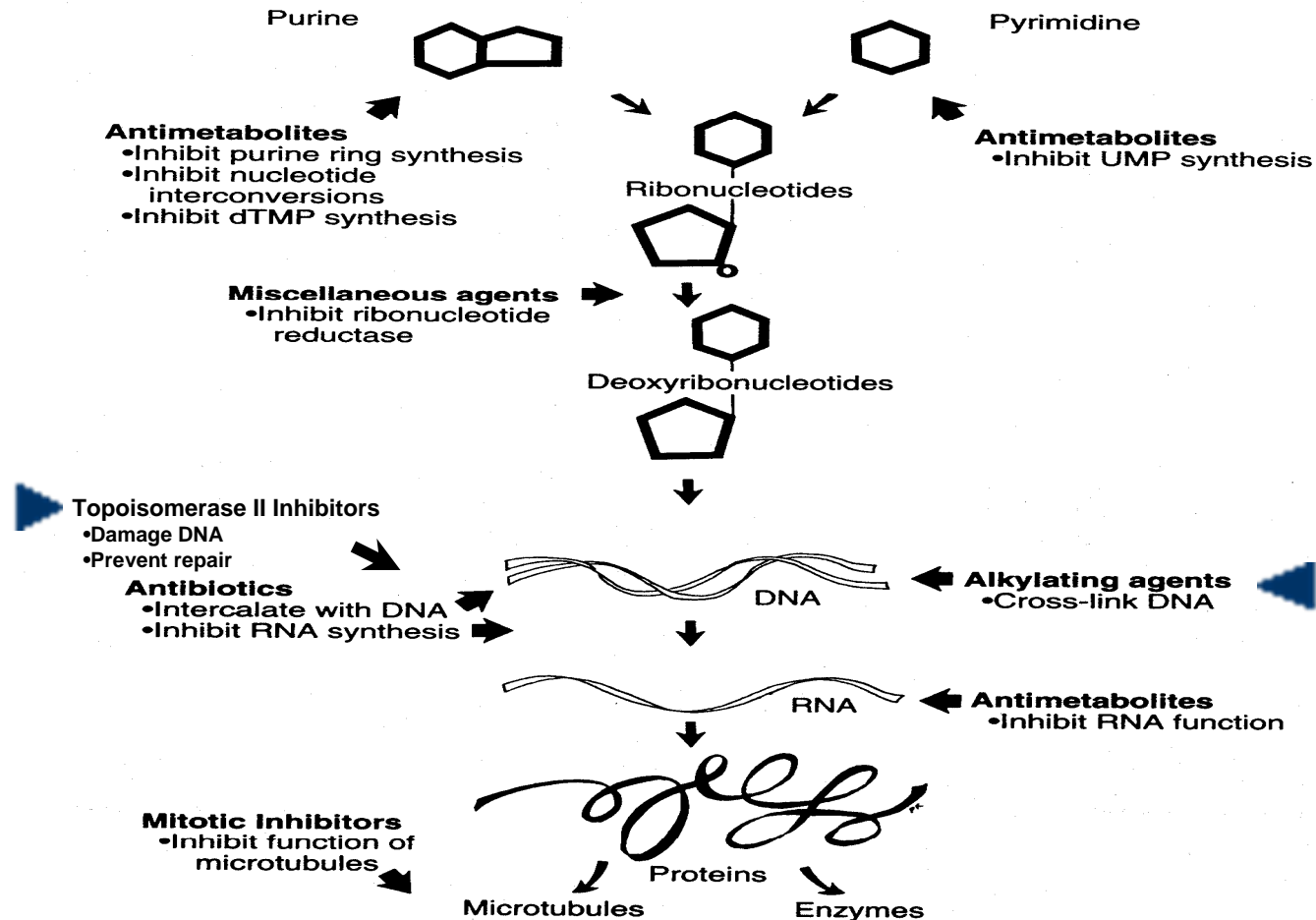


Figure 20.1. Summary of the mechanisms and sites of action of selected classes of antineoplastic agents. Adapted from Gilman GA, Rall TW, Nies AS, Taylor P, eds. The pharmacologic basis of therapeutics. 8th ed. New York: Pergamon Press, 1990:1208. (Adapted)

Developmental Toxicity and Genotoxicity of Some Common Anticancer Agents

<u>Drug Class</u>	<u>Developmental Toxicity</u>			<u>Genotoxicity</u>	
	<u>Animal</u>		<u>Human</u>	<u>PM</u>	<u>CE</u>
	<u>T</u>	<u>E</u>			
Alkylating Agents	+	+	+	+	+
Antibiotics	+	+	+	+	+
Antimetabolites	+	+	+	+	+
Mitotic Function	+	+	+	-	+
Topoisomerase II Function	+	+	+	+	+

(+) = effect seen; (-) = no effect seen. (T)=Teratogenic; (E)=Embryotoxic, (PM)=Point Mutation, (CE)=Chromosomal Effects

Severity of the Hazard

These Drugs are:

- 14(12+2) of ~110 IARC Group I Carcinogens
- 11 of Group 2A
- 11 of Group 2B
- Well documented reproductive and developmental toxicants in animals and humans (Alkylating Agents, Antimetabolites); some male-mediated
- Associated with biologically plausible health effects in studies of exposed populations

Table 1. Diseases and Drugs with a Reported Risk of Treatment-Related Myelodysplasia or AML.

Hematologic neoplasias

Multiple myeloma
Hodgkin's disease
Non-Hodgkin's lymphomas
Polycythemia vera
Essential thrombocythemia
Acute lymphoblastic leukemia

Solid tumors

Breast cancer
Lung cancer
Testicular cancer
Gastrointestinal cancer
Childhood tumors

Nonmalignant diseases

Rheumatoid arthritis
Psoriasis
Wegener's granulomatosis

Alkylating agents

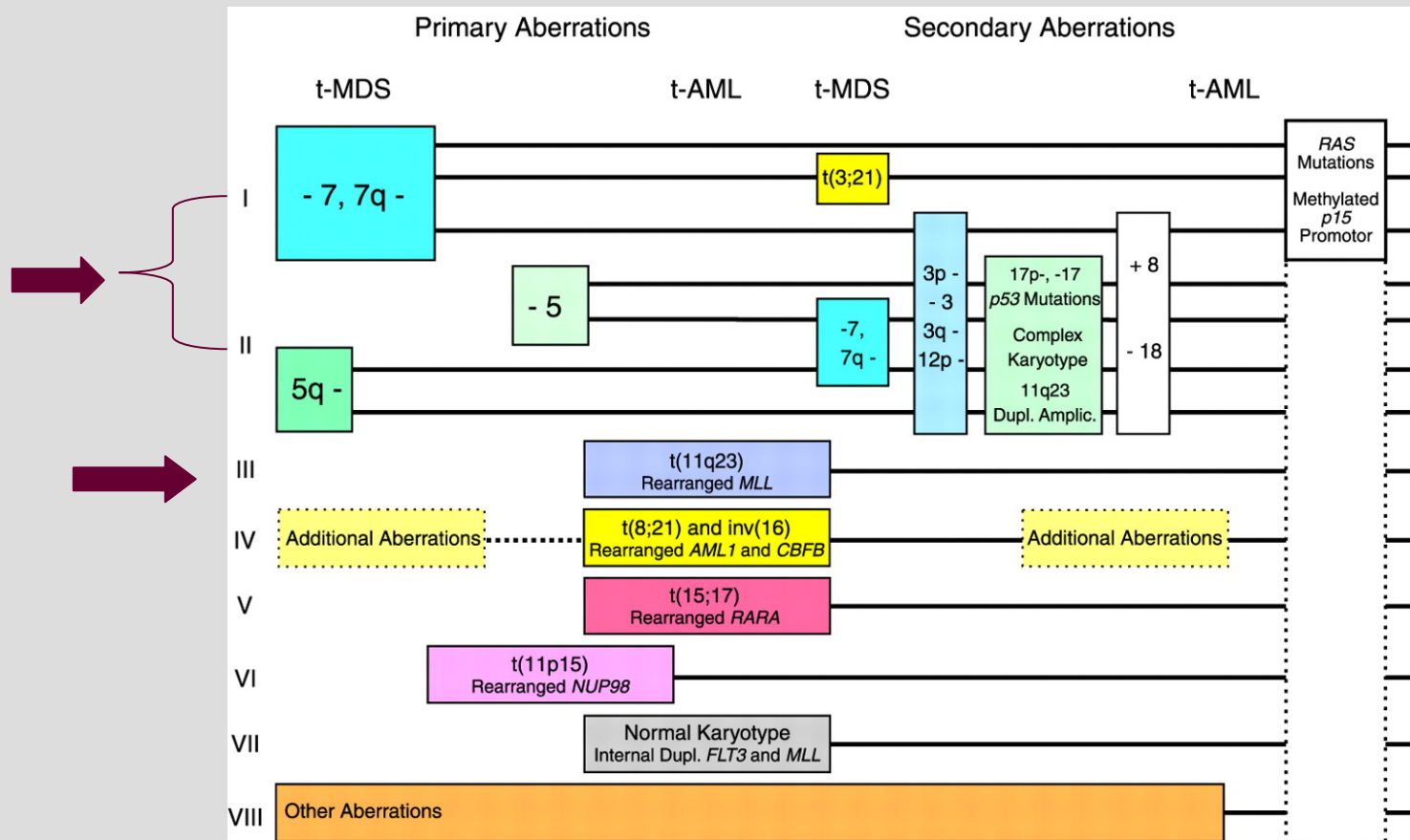
Melphalan
Mechlorethamine
Cyclophosphamide
Busulfan
Dihydroxybusulfan
Chlorambucil
Carmustine
Lomustine
Semustine
Dacarbazine
Cisplatin
Carboplatin

Topoisomerase II inhibitors

Etoposide
Teniposide
Doxorubicin
4-epi-doxorubicin
Daunorubicin
Mitoxantrone
Razoxane
Bimolane

Genetic Pathways in t-MDS and t-AML

Figure 1.



Rationale for Study

- Many positive biomonitoring studies of exposed oncology workers revealed uptake of anti-cancer drugs measured in urine, including some in non-drug handlers.
- Previous studies have shown excesses in non-specific measures of genotoxic outcomes (SCE, MN, total CAs).
- No previous study has looked for the ‘signature’ chromosomal lesions associated with t-MDS/t-AML on Chromosomes 5,7, and 11 in workers.

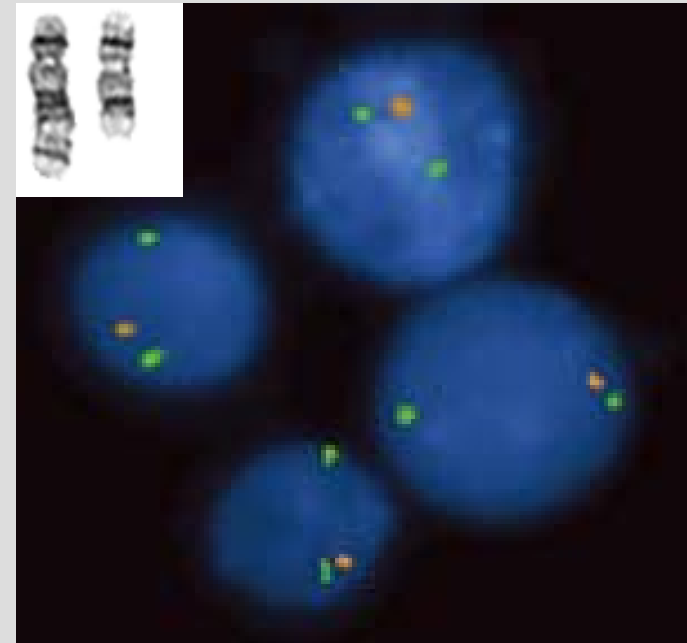
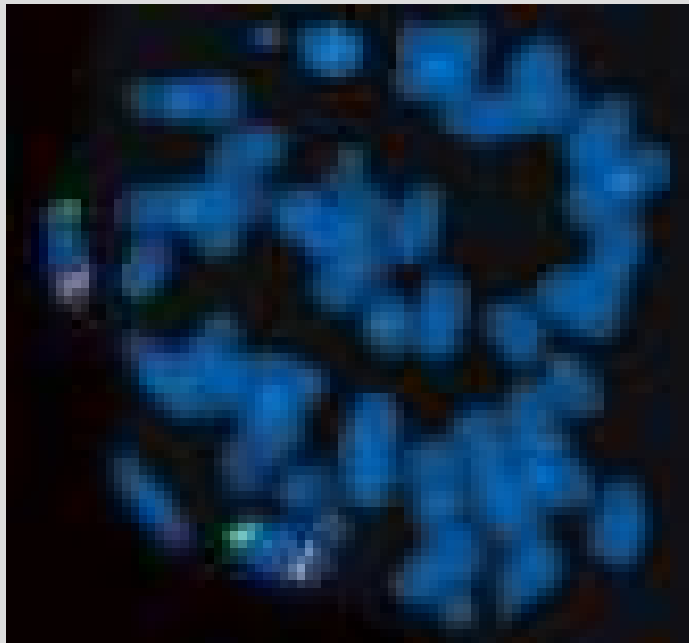
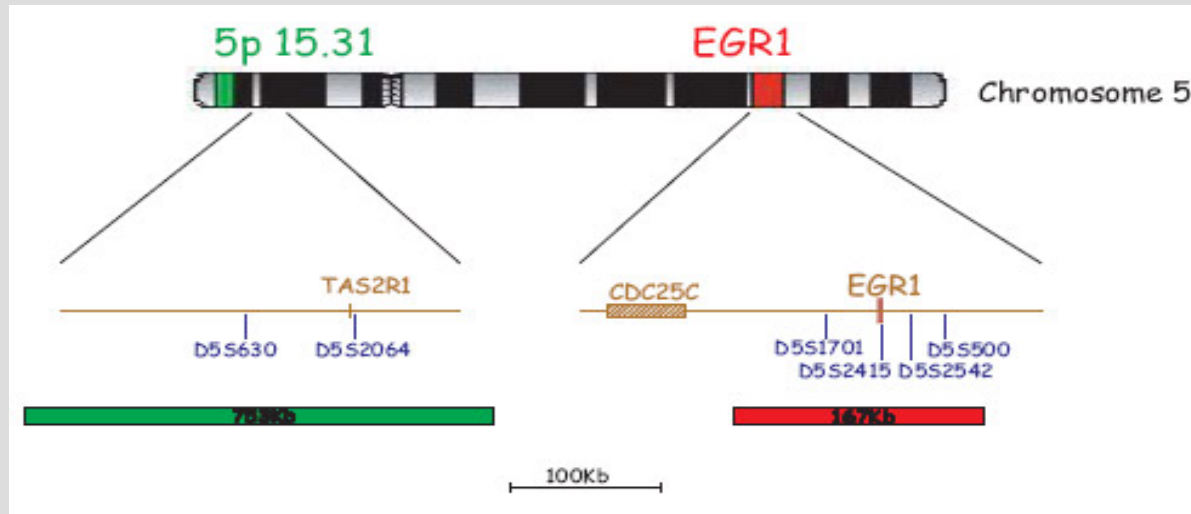
NIOSH Health Care Worker Study

- Multicenter study
- Comprehensive study of health care workers who handle antineoplastic drugs
- Environmental sampling
- Biological sampling
- Health and work history
- Six-week drug handling diary

Outcomes of Interest

- Environmental Sampling Results for 5 Drugs
- Urinary Drug Levels
- Chromosomal 5,7, and 11 Effects

FISH Detection of Deletion



Inclusion/Exclusion Criteria

- Inclusion:
 - Age 18-50
 - > 6 month history of handling drugs
 - 24hrs. working in week prior to sampling
 - Non-exposed employed in same job title w/o drug handling
- Exclusion:
 - Current smokers
 - Current/previous treatment with chemotherapeutics or XRT
 - Current treatment with other genotoxic meds. (e.g., accutane, hormones)

Diary of Drug Handling Events

- Compounding/Preparing
- Checking (Dose/calculations)
- Infusion
- IV Push
- Prime Tubing
- Spill
- Splash
- Urine/vomit exposure

TABLE 2. Exposure Characteristics of Study Population

Characteristics	Nonexposed* (N = 46)	Exposed (N = 63)
→ Total drug exposure handling frequency†		
Mean (SD)	0	153.17 (248.53)
Median		23
Minimum		1
Maximum		914
→ Alkylating drug-handling frequency		
Mean (SD)	0	36.69 (57.71)
Median		7
Minimum		1
Maximum		250
Radiation exposure in past year (mSv)		
Mean (SD)	2.77 (1.65)	3.18 (2.37)
Median	2.41	2.42
Minimum	2.4	2.4
Maximum	10.46	10.48
Environmental tobacco smoke exposure (hr/d)		
Mean (SD)	0.3 (1.24)	0.22 (1.18)
Median	0	0
Minimum	0	0
Maximum	8	9

*Nonexposed-handling frequency set to zero.

†Number of drug-handling events from 6-wk diary recordings.

TABLE 3. Drug-Handling Event Frequency by Drug Class and Job Title

Drug Class	No. Handling Events (% of Total) for Each Job Title			
	Nurse (<i>N</i> = 1809)*	Pharmacist (<i>N</i> = 3858)*	Pharmacy Technician (<i>N</i> = 3983)*	Total (<i>N</i> = 9650)*
Alkylating	441 (24.4)†	943 (24.4)	846 (21.2)	2230 (23.1)
Anthracyclines/antibiotics	147 (8.1)	289 (7.5)	440 (11.0)	876 (9.1)
Antimetabolite	373 (20.6)	885 (22.9)	662 (16.6)	1920 (19.9)
Biological	201 (11.1)	517 (13.4)	599 (15.0)	1317 (13.6)
Hormonal	3 (0.2)	0 (0.0)	5 (0.1)	8 (0.1)
Mitotic inhibitor	273 (15.1)	688 (17.8)	1048 (26.3)	2009 (20.8)
Topoisomerase II inhibitor	85 (4.7)	162 (4.2)	118 (3.0)	365 (3.8)
Tyrosine kinase inhibitors	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.0)
Other	284 (15.7)	374 (9.7)	265 (6.7)	923 (9.6)

*Total number of drug-handling events in 6-wk period by job title.

†Percent of drug-handling events by job title.

The values are represented as *N* (%).

Surface Wipe Samples

- Pharmacy



Surface Wipe Samples

- Pharmacy
 - Work surface of BSCs



Surface Wipe Samples

- Pharmacy
 - Airfoil of BSCs



Surface Wipe Samples

- Pharmacy
 - Counter tops



Surface Wipe Samples

- Pharmacy
 - Waste containers



Surface Wipe Samples

- Pharmacy
 - Drug trays



Surface Wipe Samples

- Pharmacy
 - Pass-through windows



Surface Wipe Samples

- Pharmacy
 - Floors



Surface Wipe Samples

- Nursing
 - Nursing Station
 - IV Bag
 - Storage
 - Floors
 - Patient Rooms
 - Waste Containers



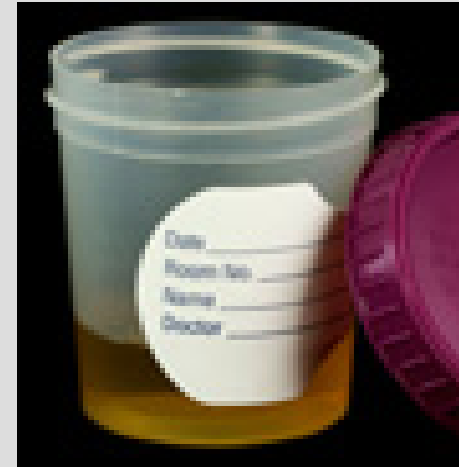
Results-Wipe Samples

- Total Number
 - Pharmacy-80
 - Nursing-65
- >LOD for at least 1 Drug
 - Pharmacy-75%
 - Nursing-43%



Measurement of Drugs in Urine

- Drugs Measured
 - Cyclophosphamide
 - Paclitaxel
- Collection period
 - Last 4 hours of work shift (pooled)
 - 4 Hours post-shift (pooled)



Biologic Monitoring Results for drug in urine

- 2/63 samples positive for cyclophosphamide
- 1/63 samples positive for paclitaxel

Statistical Analyses

CA frequency examined as a function of frequency of drug handling:

1. Categorical variable (no, lo, hi) exposure
2. Continuous variable (# drug handling events)

No difference in CA frequency was observed between the exposed and non-exposed when analyzed by exposure group.

TABLE 4. Chromosomal Damage Frequency* Among HCWs Exposed to Anticancer Drugs by Exposure Category

	No Exposure Subjects With No Events (N = 46)	Low Exposure		High Exposure	
		Subjects With 1–153 Events (N = 46)	P†‡	Subjects With >153 Events (N = 17)	P†§
Numeric					
Chromosome 5 or 7	0.07 (0.25)	0.04 (0.21)	0.86	0.24 (0.44)	→ 0.08
Chromosome 5	0.02 (0.15)	0.02 (0.15)	0.84	0.12 (0.33)	0.13
Chromosome 7	0.04 (0.21)	0.02 (0.15)	0.62	0.12 (0.33)	0.18
Chromosome 11	0.09 (0.28)	0.07 (0.33)	—	0.18 (0.39)	—
Structural					
Chromosome 5 or 7	0.07 (0.33)	0.07 (0.25)	—	0.24 (0.56)	—
Chromosome 5	0.02 (0.15)	0.04 (0.21)	0.19	0.18 (0.53)	→ 0.04
Chromosome 7	0.04 (0.29)	0.02 (0.15)	—	0.06 (0.24)	—
Chromosome 11	0.07 (0.25)	0.09 (0.28)	0.79	0.06 (0.24)	0.91
Total changes					
Chromosome 5 or 7	0.13 (0.40)	0.11 (0.31)	0.56	0.47 (0.80)	→ 0.02
Chromosome 5	0.04 (0.21)	0.07 (0.25)	0.37	0.29 (0.59)	→ 0.01
Chromosome 7	0.09 (0.35)	0.04 (0.21)	0.85	0.18 (0.39)	0.33
Chromosome 11	0.15 (0.42)	0.15 (0.42)	0.92	0.24 (0.44)	0.26

Data are represented as mean (SD). Bold values are those reaching statistical significance.

*Per 200 cells counted.

†P value result from comparison between the low-exposure group and no exposure group.

‡Reported P values are from χ^2 test.

§P value result from comparison between the high-exposure group and no exposure group.

||Insufficient data to estimate standard errors/P values using generalized linear models.

¶Missing p or translocation/deletion/break/extra copy.

Table 5. Incidence Rate Ratios^a (IRR) of Chromosome Abnormalities at Select Drug Handling Event Levels

Location of chromosome abnormality	100 event IRR	(95% CI)	500 event IRR	(95% CI)	p value^b
Chr 5	1.24	(1.05-1.47)	2.94	(1.26-6.85)	0.01
Chr 7	1.13	(0.91-1.42)	1.88	(0.61-5.77)	0.27
Chr 5 or 7	1.20	(1.05-1.37)	2.49	(1.29-4.81)	0.01
Chr 11	1.04	(0.81-1.34)	1.24	(0.36-4.35)	0.73

^aIRR-describes association between chromosome abnormality rates predicted by the model at select drug handling frequencies compared to chromosome abnormality rates at 0 drug handling events (controls)

^breported p-values are from chi-square test

Table 6. Incidence Rate Ratios^a (IRR) of Chromosome Abnormalities (alkylating agents only) Event Levels

Location of chromosome abnormality	100 event IRR	(95% CI)	200 event IRR	(95% CI)	p value^b
Chr 5	2.92	(1.35-6.32)	8.54	(1.83-39.89)	0.01
Chr 7	2.31	(0.83-6.41)	5.33	(0.69-41.12)	0.11
Chr 5 or 7	2.62	(1.46-4.71)	6.86	(2.13-22.14)	0.001
Chr 11	1.17	(0.38-3.61)	1.37	(0.14-13.02)	0.79

^aIRR-describes association between chromosome abnormality rates predicted by the model at select drug handling frequencies compared to chromosome abnormality rates at 0 drug handling events (controls)

^breported p-values are from chi-square test

Biologically important exposure to genotoxic drugs is occurring in oncology work settings despite hospital “endorsement” of ‘Safe Handling Practices’