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Summary Report of NIOSH Industrywide
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Occupational Exposure to Cancer Chemotherapeutic Agents in Pharmacists and Nurses

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I. ABSTRACT

This report describes the results of a study of the presence of mutagenic substances in the urine of pharmacists, pharmacy technicians and nurses engaged in the preparation, handling and administration of cancer chemotherapeutic agents at the Memorial Sloan - Kettering Cancer Center, New York City. Single urine samples (pooled from all urine collected during one 8 hour daytime shift) were obtained from exposed and control hospital personnel and subsequently analysed for mutagenic activity by the Ames bacterial assay using TA98 and TA100 strains of Salmonella typhimurium with S-9 rat liver microsome mix. The criterion for inclusion in the exposed group was the regular handling, preparation or administration of cancer chemotherapeutic agents: 19 of 21 subjects had handled these drugs within the 72 hours preceeding urine collection and 17 on the day of urine collection.

Using analysis of variance, no significant differences were observed with respect to mean numbers of revertant TA98 or TA100 colonies per plate (using both filter-sterilized urine and urine concentrate) between exposed and non-exposed personnel or between job categories (nurses, pharmacists, pharmacy technicians). Smokers had significantly greater mutagenic activity in urine compared to non- or ex-smokers for the TA98 strain. Personnel in this study used vertical laminar airflow biological safety cabinets and personal protective equipment when handling these agents.

In view of the known mutagenicity, potential carcinogenicity and teratogenicity of chemotherapeutic agents, together with the finding of positive urine mutagenicity in other studies where employees had less adequate protection, strict adherence to the use of containment devices, personal protection and specified operating and disposal procedures for all personnel who have contact with these agents is strongly recommended.

II. Introduction

The rationale for the examination of workers using cancer chemotherapy agents for evidence of exposure to mutagens is as follows:

1. Ames et al (1) and other workers have consistently shown that the great majority of substances of known carcinogenic potential (in animals and/or humans) are also mutagens, as shown by the Ames bacterial mutagenicity assay. McCann et al (2) and McCann and Ames (3) showed a 90% correlation between carcinogenicity and mutagenicity for 300 known carcinogens; Rinkus & Legator (4) showed a 77% correlation for 465 known or suspected carcinogens, and Purchase et al (5) showed a 93 % correlation for 120 carcinogens and noncarcinogens. The finding that many known carcinogens are mutagens has led to the thesis that the common mechanism of mutagenesis and carcinogenesis may lie in faulty DNA repair.[See review by Devoret (6)].

Mutations arise as a result of damage to the DNA molecule which is not successfully repaired by the normally effective mechanisms of excision, postreplication repair or photoreactivation. Subsequent replication leads to the incorporation of incorrect DNA bases, thus producing a heritable mutation. Mutations may occur in the DNA of germ cells and/or somatic cells, thereby theoretically increasing the risk of genotoxicity, carcinogenicity and reproductive effects (fertility impairment, fetal deaths, congenital malformations and heritable mutations in offspring).

2. Chemotherapy agents may be alkylating agents, antibiotics, mustards or hormones. They exhibit their potent cytotoxicity by their ability to bind to and disrupt the normal function of DNA (7,8,9,10). Due to their mechanism of action, they exhibit both mutagenic and carcinogenic activity. A number of cancer chemotherapeutic agents have been shown to possess mutagenic activity in the Ames Salmonella mutagenicity test (11,12,13).

3. Many cancer chemotherapeutic agents, by a phenomenon known as Haddow's paradox, (14) have been shown to be carcinogenic in animal models. For example, daunomycin and adriamycin have been shown to induce mammary and renal tumors in rats after single i.v. doses (15,16,17) and in mouse fibroblasts in vitro. Weisburger et al (18) found a range of commonly used chemotherapy agents to be carcinogenic

in rats. The literature has been reviewed by Schmahl and Habs (19) and Harris (20) who conclude that, despite marked differences in test procedures, doses and strains of rodent, the carcinogenic potential of these drugs is unequivocal, particularly in the case of the alkylating agents.

4. There is evidence that these agents may cause secondary cancers in patients undergoing chemotherapy (20,21,22,23). For example, bladder tumors have been observed in patients receiving cyclophosphamide (24) and chlornaphazin (25), myelogenous leukemia following melaphan treatment (22) and thio-tepa treatment (26), myeloblastic leukemia following thio-tepa (22), and myelocytic leukemia in patients with Hodgkin's disease following radio-and chemotherapy (23).

5. Finally, there is some evidence that exposure to mutagens may be associated with other conditions such as aging and vascular disease (27, 28) as well as with direct acute effects in the form of skin and eye irritation and allergic responses.

In summary, therefore, a large number of commonly used chemotherapy drugs have been shown to be mutagenic in bacterial assay systems and in animal models. Some 30 cancer chemotherapy agents are currently commercially available, which are administered to an estimated 200,000 - 400,000 patients annually (29). Several thousands of individuals are engaged in

their manufacture, preparation, handling and administration; thus the extent of exposure of these individuals and the means to control exposure have become issues of considerable concern. There are several methods by which exposure to mutagens can be assessed in humans:

1. Chromosome aberrations or sister chromatid exchange (SCE). Mutagenic carcinogens tend to produce morphologically recognizable cytogenetic damage, so that measurements of increased rates of chromosome aberrations or SCE have become increasingly used as indicators of mutagen exposure.

2. Urine mutagenicity. Yamasaki and Ames (30) and later Van Doorn et al (31) have demonstrated that humans exposed to the known mutagen-carcinogens in cigarette smoke excrete these in their urine, by finding positive mutagenicity of concentrated urine in the Ames Salmonella test. The evaluation of the mutagenicity of urine is a relatively simple and non-invasive method suitable for initial screening of populations for exposure to mutagens, in comparison with the more complex and expensive methods of chromosome aberrations and SCE frequency analysis (which measure the effect of exposure).

Recent studies using both methods have been conducted to assess the potential exposure of persons handling or receiving chemotherapy drugs (32-36). Lambert et al (34) for example, reported significant increases

in SCE frequency in 7 of 19 patients undergoing cancer chemotherapy. Waksvik et al. (35) demonstrated an increase in chromosome gaps and a slight increase in SCE frequency among oncology nurses and Norppa et al. (36) have shown an increase in the frequency of SCE among nurses handling chemotherapy drugs and patients receiving them.

The urine of cancer chemotherapy patients has been shown to exhibit marked mutagenicity in reverse mutation and mitotic gene conversion assays in yeast (37) and the Ames Salmonella test (38). Falck et al. (39) first measured urine mutagenicity among nurses who administered cancer chemotherapy drugs and a control group of office clerks and psychologists. Concentrates of urine collected on Thursday and Monday morning were tested by a bacterial fluctuation test using tryptophan - dependent Escheria coli or histidine auxotrophic Salmonella typhimurium (strains TA 98 & TA 100) with rat liver microsomes (S9 mix). The mutagenic activity of the nurses' Thursday urine samples was greater than that of the Monday samples and both were positive relative to the controls. Staiano et al. (40) measured urine mutagenicity among hospital pharmacist from samples collected 2 days before, during drug preparation and 24 and 48 hours afterwards; no change in urine mutagenicity was observed. Wilson and Solimando (41) also reported no change in the mutagenic activity of urine among several pharmacists preparing such drugs.

Most recently, Nguyen et al (42) conducted a longitudinal study of 8 pharmacy technicians engaged in the preparation of chemotherapy drugs and 3 pharmacy personnel who did not handle the drugs; urine mutagenicity was tested using the Ames S. typhimurium assay (strains TA 98, TA 100 and TA 1535).

Eight day continuous urine samples were collected (2 days before, during and up to 2 days after exposure). Exposed subjects showed positive urine mutagenicity (determined as two times the number of background revertant colonies per plate) between day 3 and 4 and a return to background by day 8 when using horizontal laminar flow cabinets for drug preparation. The use of a vertical laminar flow type of cabinet resulted in a reduction in the mutagenicity of the urine but not the use of gloves and masks in the horizontal flow cabinets.

It is clear from the above review that the extent of exposure of hospital personnel to chemotherapy agents using different control measures has yet to be clarified; it is also clear that under certain circumstances exposure occurs as shown by both chromosome aberration and SCE studies and by urine mutagenicity studies. This study describes the evaluation of exposure to chemotherapy agents among hospital personnel in a major cancer treatment center using the urine mutagenicity assay developed by Ames et al (1) to measure exposure.

III. Methods

a) Study design.

A cross sectional study design was employed using pharmacists, pharmacy technicians and nurses who had been engaged in the preparation, handling and/or administration of cancer chemotherapy agents within the 72 hours prior to urine collection as the exposed group, and pharmacists, pharmacy technicians and nurses not so exposed as controls. A list of the major antineoplastic drugs regularly prepared in the pharmacy is given in Table 1. The staff would also normally deal with a number of other drugs in a given shift.

The individuals in the group delineated above were asked to participate and to sign a consent form (Appendix A). There was one refusal. Participants were given a self-administered questionnaire to complete to provide information on work history, smoking status, health status and drug use (Appendix B) and asked to give a urine sample.

A timed 8 hour urine sample was collected from both groups. Participants were requested to collect all urine during the study period except for the first morning void, which was to be discarded. Participants were also instructed to refrain from drinking or eating saccharin containing beverages, candy or gum. Urine was collected in polyurethane containers,

divided, labelled and frozen in dry ice prior to dispatch to the analytical laboratory. Samples were collected from groups as shown in Table 2.

b) Analysis of urine for mutagenicity.

Samples were analysed by Dr. Richard Everson, National Institute for Environmental Health Sciences, N. Carolina.

Urine was analysed for mutagencity using the Ames Salmonella- mammalian microsome assay (1), the most widely used and validated microbial assay available. The principle of the assay is as follows. Various test strains of Salmonella typhimurium have been developed which are histidine deficient but susceptible to reversion to histidine producing colonies in the presence of a wide variety of mutagens. Histidine deficient bacteria can be plated onto agar containing only a trace of histidine (see below) so that only those which revert to prototrophy can reproduce and form colonies. Thus the number of revertant colonies appearing in the presence of a known or suspected mutagen can be compared with the number of spontaneous revertant colonies appearing on plates without the mutagen. A trace of histidine is added to the agar so that some bacterial growth is permitted: this is the background lawn. The presence or absence of this lawn provides a means to check the direct bacterial toxicity of the mutagen; the lawn on the test plate should be the same as that on the

control plate. (If the mutagen is highly bacteriotoxic, the surviving bacteria have more histidine available and may reproduce and thus be mistaken for revertant colonies.) As a check on the reversion properties of each strain and each experimental preparation, known mutagens should be included as positive controls; using known mutagens which require metabolic activation also serves to check on the activity of the S-9 mix (see below). Examples of such mutagens are 2-acetyl aminofluorene and aflatoxin B.

In the mammalian system, potential chemical carcinogens and mutagens frequently require activation via metabolism by the family of cytochromes found in liver (and to a lesser extent kidney and lung) cell microsomes. The addition of the 9000 g supernatant (S-9) microsomal fraction of homogenized rat liver (from rats whose liver cytochrome content has been increased by induction with agents such as Aroclor 1254) to the agar plate replicates this mammalian metabolic pathway in vitro. Finally, since some mutagenic metabolites are excreted as beta-glucuronide conjugates in mammalian systems, beta-glucuronidase may be added to the plate to split the conjugate. Yamasaki and Ames (30) developed a method for concentrating mutagens in urine using a nonpolar resin column (XAD-2). This facilitates the application of a range of doses of microgram quantities of urine residue taken up in the non-mutagen solvent dimethyl sulfoxide (DMSO) after extraction; this method also removes histidine from the urine. The materials and methods used to prepare and assay urine samples in this study are described below.

c) Materials and methods. (R. Everson)

Chemicals

Aroclor 1254 was purchased from Analabs, Inc., North Haven, Connecticut; 2-acetylaminofluorene, glucose-6-phosphate, and beta-glucuronidases [types VIII (bacterial in 50 percent glycerol solution) and H-1 (Helix pomatia, partially purified powder)] from Sigma Chemical Co., St. Louis, MO.; NADP and NADPH from Boehringer Mannheim, Indianapolis, Ind. Nutrient broth was obtained from Oxoid Corp., London, England; agar was from Difco Laboratories, Detroit, Mich. Other chemicals were the purest available commercial reagents.

Bacterial Strains

S. typhimurium tester strains TA 98, and TA 100 were generous gifts of Dr. Bruce Ames, University of California at Berkeley. Periodic testing revealed appropriate sensitivity to crystal violet and resistance to ampicillin.

Media

Sterile media and bacteriologic plates were prepared by the National Institute of Environmental Health Sciences Media Production Unit. These

included Phosphate Buffered Saline, pH 7.4 (PBS); nutrient broth (25 g/l Oxoid #2); top agar (0.6% Difco minimal plates (20 ml/1 50 times concentrated Vogel-Bonner salts, 1.5% Difco agar, 3.1 % glucose, 3.0 ml/1 biotin) with 20 ml of media per plastic petri dish.

Urine Specimens

Urine samples were frozen immediately after collection and stored at -80°C until use. Samples were thawed and filtered with Whatman No. 1 filter paper. An aliquot was taken and filter sterilized using 0.45 micron filters (Millex, Millipore Corp., Bedford, Mass.); this aliquot was also used to measure pH and creatinine levels. The remainder of the urine was passed through Glass Econo columns (0.7 cm x 10cm, Bio-Rad), Richmond, Ca.) containing 700 mg of a nonpolar resin (XAD-2, Applied Science Labs., State College, Pa.) at a rate of 1.5 to 2.0 ml per minute. Flow was regulated with a three way metering stopcock (Bio-Rad). Columns were prepared before use by rinsing with 20 ml each of acetone and methanol, and 300 ml of distilled water. After the urine was passed through the column, the column was purged with nitrogen for 30 sec. The column was then rinsed with 10ml of distilled water to remove any residual histidine and then again purged with nitrogen for 30 sec. The components on the column were eluted with 10ml of methanol into a glass vial at a rate of approximately 1.0 ml per minute. The methanol was evaporated under a slow stream of nitrogen at a temperature of 37° C to complete dryness and frozen extract was resuspended in DMSO at the rate of 0.4 ml DMSO per 100

ml urine (i.e., each 0.1 ml extract tested is equivalent to 25 ml urine). Creatinine assays were done using materials and methods included in a reagent kit provided by Sigma Chemical Company.

Preparation of Rat Liver S-9

Procedures were a modification of the technique reported by Ames and coworkers (1). Aroclor 1254 was administered to Sprague-Dawley male rats (obtained from the National Institute of Environmental Health Sciences Animal Supply) as a single intraperitoneal dose of 500 mg/kg dissolved in corn oil. Five days later animals were killed and all subsequent steps in the isolation of subcellular fractions were performed at 0-4 C. Livers were placed in 0.15 M KOH, washed, minced, and homogenized in 3 times their weight of KOH by a polytron (Model Brinkmann Inst., Westbury, N.Y.). Homogenates were centrifuged at 9000xg for 20 minutes and the supernatant frozen on dry ice and stored at $-80^{\circ}C$.

Mutagenesis Assays

The activation mixture (S-9 mix with beta-glucuronidase) was prepared such that each mutagenesis plate received 0.1 ml liver S-9 supernatant, 0.5 mg NADPH, 1.0 mg NADP, 1.5 mg glucose-6-phosphate, 0.125 ml 0.4 M phosphate buffer (45.4 g/l Na_2HPO_4, 9.6 g/l Na_2HPO_4, 9.8 g/l KCl,

pH adjusted to 7.4), 0.125 ml $MgCl_2$ solution (6.5 g/l), 0.5 mg type H-1 beta glucuronidase (400,000 units/g), and 0.05 ml type VIII beta-glucuronidase (14,000 units/ml). This mixture was filter-sterilized using 0.45 micron filters. Multiple 2.5 ml aliquots of top agar containing 0.045 mM histidine were prepared at 45° C. Except as indicated 0.05 ml of urine extract, 0.1 ml of a fresh overnight bacterial culture, and 0.4 ml of activation mixture were added rapidly (in that order) to the top agar, mixed, poured and distributed evenly on the Vogel-Bonner minimal media plates. Duplicate plates were used for all mutagenesis assays. Plates were incubated at 37°C for 44 hours and the number of colonies per plate (histidine revertants) determined manually for counts less than 100 or by an electronic colony counter for higher values (Count-All model 600, Fisher Scientific Co., Pittsburgh, Pa.).

Quantification of the Bacterial Lawn

Toxicity on the background lawn was determined by one of two methods. The first method is that recommended by Ames and coworkers (1), plating approximately 500 bacteria per plate with an excess of histidine, the bacteria, urine sample and S-9 mixture and comparing the count to a control plate without any urine on it. By taking a ratio of test to control counts the percent survival can be determined. Another method was used in some cases to directly determine the number of surviving bacteria in the background of some plates. Three areas free of visible colonies

that were as close to symmetrically distributed over the plate as possible were identified under a dissecting microscope. A cylinder from each of these areas that was free of colonies but contained the background lawn was taken using a sterile 5 ml ampoule and sterile forceps. Three cylinders from each of two plates were suspended in 4.0 ml PBS in 17 x 100 mm plastic test tube at room temperature. These plugs were fragmented using a previously mentioned Brinkmann Polytron on #5 setting. 6.0 ml of PBS were added, the suspension was mixed and diluted with PBS usually 800 fold and an aliquot plated using top agar containing an excess of histidine. Plates were counted as described previously.

IV. Results

Descriptive statistical information obtained from the questionnaires completed by study participants is summarized in Table 3.

The number of revertant colonies per plate were determined for (i) TA 98 and (ii) TA 100 strains of S. typhimurium under the following conditions:

1) 300 ug filter-sterilized urine + S-9 mix.
2) 50 ug urine extract + S-9 mix
3) 100 or 150 ug urine extract + S-9 mix
4) DMSO + S-9 mix
5) AAF (25 and 50 mg) + S-9 mix

Both filter sterilized urine and resin- extracted urine were tested for mutagenicity to check for any loss of mutagenic activity during resin extraction. The creatinine concentration per 50 ug urine extract was determined and results for the 50 ug extracts expressed as number of revertant colonies/mg creatinine. The results for 300 ug filter sterilized urine and 50 ug urine extract are presented by exposure group and smoking group in Tables 4 and 5, respectively. For 50 ug urine extracts, the numbers of revertant colonies/plate of TA98 and TA100 for individual nurses and pharmacists by exposure group and smoking status are shown. The toxicity of the urine (50 ug extracts) was determined according to the methods described above. The percentage survival rate, (i.e. the ratio of the revertant colonies counts with and without 50 or 150 ug urine extract x 100) is given for exposed and non-exposed groups in Table 6, and by smoking groups in Table 7.

These data were first tested for significant differences by:

(I) job title (nurse, pharmacist, pharmacy technician)

(II) exposure category (exposed, non-exposed)

(III) interaction of job title and exposure category

(IV) smoking status (current smokers, non-or ex-smokers) using analysis of variance. The results are shown in Table 8.

No significant differences were observed between exposed and unexposed groups or between job categories with respect to:

a) the number of TA 98 or TA 100 revertants colonies/ plate with 300 ug filter sterilized urine or per mg creatinine with 50 ug urine extract.

b) age

c) total years worked

d) mg creatinine per 50 ug urine extract

A significant difference ($p=0.01$) was found between current smokers and non or ex-smokers with respect to the number of TA 98 revertants/mg creatinine using 50 ug urine extracts. The observed increase in the mutagenic activity of smokers supports the findings of a number of workers, notably Yamasaki and Ames (30). In the case of individual results, evidence of positive mutagenicity was defined as a urine sample which yields 2.5 times the number of revertant TA 98 or TA 100 colonies/plate obtained using the S-9 mix and DMSO solvent alone. The number of individuals showing positive urine mutagenicity thus defined by exposure group and smoking status is shown in Table 9.

Testing for the direct toxicity of the urine showed that there was no statistically significant effect on the bacteria from filter-sterilized urine and urine extracts except with respect to exposure group and by job

title for TA 100's using 50 ug urine extract per plate (Table 8). No significant difference was seen at 150 ug urine extract per plate, however. The data in Table 6 show that urine from exposed pharmacy technicians and unexposed pharmacists appears to be moderately directly toxic to TA 100 S. typhimurium at both 50 ug and 150 ug urine extract per plate. One may postulate that these groups may be excreting some bacteriotoxic agents into their urine e.g. an antibiotic or its metabolite. Results for TA 100 plates for these groups should be interpreted with caution.

(Note: In a further analysis, data from pharmacists and pharmacy technicians were combined into one job category, and the analyses of variances described above repeated. Again, no significant differences were observed between exposed and unexposed groups or by job title with respect to the number of TA 98 or TA 100 revertants/plate with either 300 ug filter-sterilized urine or 50 ug urine extract (Table 10). Further, differences in % survival of TA 98 and TA 100 colonies by exposure group and job title were not significant when data from pharmacists and pharmacy technicians were combined to form one job category).

Everson (personal communication) performed t-tests to compare differences in mean numbers of revertants (for 50 ug urine extracts) between a) exposed and unexposed subjects and b) each of the 6 groups (i.e. 3 job

categories by exposed/unexposed status) and the solvent (DMSO) controls (N.B. Note that 2 pharmacy technicians who regularly handled chemotherapy drugs, but who had not done so within the 72 hours preceding urine collection, were included in the unexposed group in this analysis). As in the analyses of variance reported above, no significant differences were found between exposed and unexposed subjects' results, but a slight, consistent elevation in the numbers of revertants were found for all (exposed and unexposed) groups when compared with the DMSO solvent controls and for both smokers and non-smokers (Table 11); most of these differences were statistically significant. Everson states that a number of procedures were used to check for false positives, i.e., whether such elevations may result from steps used to produce the urine extracts; no evidence of such an artifact was found, suggesting that the differences between extracts and solvent controls may be due to urinary excretion of small amounts of mutagen(s) by a large proportion of the subjects tested. Information regarding caffeine, saccharin and medication consumption from the questionnaire data indicate that 90% of the sample regularly consumed caffeine and/or saccharin and approximately 50% medications (unspecified). Data on the dietary consumption of other potential mutagens (eg. bacon) was not collected: the question of the potential source of mutagenicity in the urine of these subjects therefore remains to be resolved.

IV. Discussion

Despite the discovery of the carcinogenicity of cancer chemotherapeutic agents 30 years ago by Haddow et al (14), until recently surprisingly little attention has been paid to the question of whether or not involuntary exposure to these agents should be controlled. Exposure to cancer chemotherapeutic agents is of concern in terms of both potential increased risk of carcinogenic, mutagenic and reproductive effects and of direct effects such as skin, eye and mucous membrane irritation and allergic responses. Following the positive findings of Falck et al (39) who first reported an increase in urine mutagenicity amongst oncology nurses, a number of pharmacists (13,43-45) have advocated more stringent precautions to minimize exposure on the grounds that, although the biological significance of chronic low level exposure to these agents is unknown at present, the prudent course of action is to minimize unecessary exposure.

In the preparation and dispensation of cancer chemotherapeutic agents, four factors have to be taken into account (43,44):

a) the accuracy and appropriateness of the drug and dose;
b) the sterility of the parenteral agents;
c) the safety of personnel preparing chemotherapy agents;
d) the proper disposal of chemotherapy waste.

In 1980, Hoffman (44), Director of Pharmaceutical Services at the hospital where the present study was conducted, recommended the use of biological safety cabinets (which have downward vertical flow), to ensure both an aseptic environment for the preparation of sterile doses and adequate protection for the person preparing the drug. Horizontal laminar flow hoods, also referred to as "clean benches", are widely used by pharmacists; they ensure sterility for drug protection but do not prevent exposure to aerosols generated during drug preparation. He also recommended the use of sterile gloves and alcohol swabs to minimize the potential for contact by the person administering the drug. In 1981, a joint report of the National Institutes of Health (NIH) Division of Safety in collaboration with the NIH Clinical Center Pharmacy and the National Cancer Institute (45) contained specific recommendations for the handling of chemotherapeutic drugs. These recommendations have been recently published by the NIH in a leaflet form designed for public information (46). With respect to containment, the use of a Class II vertical laminar flow biological safety cabinet is recommended to provide both operator drug protection and an aseptic environment. The Society of Hospital Pharmacists of Australia (47), the Canadian Society of Hospital Pharmacists (48) and the American Society of Hospital Pharmacists (49) also recommend the use of such vertical laminar flow biological safety cabinets during drug preparation. Further, according to Harrison (13), Kruse considers that chemical carcinogens should only be handled in a Type B Class II vertical laminar flow cabinet which is designed to vent 70% of

the work zone air to an exhaust system and thence to the outside air; the Type A cabinet allows up to 70% of the airflow to be recirculated through the work zone. This view is supported by earlier NIH guidelines on laboratory safety (50) which recommend that Type B rather than Type A cabinets " can be used with dilute preparations of chemical carcinogens, of low level radioactive materials and of volatile solvents..." and by experimental models of airflow in these cabinets by Stuart et al (51); however, other biosafety experts consider that either Type A or B cabinets may be suitable for the preparation of antineoplastic agents where these are relatively non-volatile. (D. Weathers, CDC, personal communication).

If the measurement of urine mutagenicity using the Ames bacterial assay is a sufficiently sensitive measure of mutagen exposure and if the study designs employed to date are adequate to detect an exposure if present, the studies thus far available appear to support the recommendation that vertical flow biological safety cabinets as opposed to horizontal laminar airflow (or no) hoods be used, together with gloves and gowns. In the present study, vertical laminar flow biological safety cabinets are used together with some or no personal protective equipment by the pharmacy personnel and nurses. No evidence of increased exposure to mutagenic agents was found in this group. The sample sizes used in this survey are sufficient only to detect an approximately three fold or larger increase in revertants in exposed compared to control urine samples. Such increases have been observed in other studies of this type, and are

frequently exceeded among smokers, but these limitations on the sensitivity of the method to detect changes in mutagen excretion in small groups should be noted. The collection of a single one shift urine sample should be adequate to ascertain whether or not significant exposure has occurred during drug handling on the day of sampling, since the pharmacokinetics of drug absorption and excretion indicate rapid clearance of these agents within 24 hours of exposure (Everson, personal communication). All except two of the exposed group had handled chemotherapy drugs on the day of urine collection; of these, 71% had also prepared or handled drugs on the previous two days. However, repeated urine sampling over several days of drug handling would be necessary to provide a more representative sample of exposure. The population studied by Staiano et al (40), who also reported negative findings, used Class II Type A vertical flow hoods during drug preparation. Perhaps the most comprehensive study to date is that of Nguyen et al (42) who reported a decrease in urine mutagenicity following a change over from horizontal to vertical flow hoods. Wilson and Solimando (41), who reported negative urine mutagenicity among pharmacists, stated that laminar flow hoods and aseptic techniques were used in the preparation of drugs to minimize contact with the material. (Note: A recent report by Reynolds et al (52) indicated that acute adverse reactions to the drug AMSA, experienced by pharmacists when preparing the drugs in horizontal flow hoods, were prevented by changing the operation to a vertical flow hood, supporting the conclusion that the latter protects the operator from drug exposure).

The findings of Falck et al (39), who reported positive urine mutagenicity among oncology nurses who administered these drugs, point to the need for adequate personal protection not only during drug preparation but also during subsequent handling and administration. Direct skin contact should be avoided both because absorption of the drug through the skin is a potential route of exposure and because several of these agents are powerful vesicants and may cause skin irritation and blistering. Thus the guidelines cited above (43-49) all recommend the use of personal protective clothing (surgical gowns and disposable surgical gloves) and stringent work practices for the handling and disposal of drug products and drug contaminated materials and equipment.

To date, neither NIOSH nor OSHA have promulgated specific recommendations or regulations concerning exposure to cancer chemotherapeutic agents; none of these agents are among the 18 confirmed carcinogens to which federal regulations apply, and only two (mechlorethamine and dacarbazine) are included in OSHA's "List of Substances which may be Candidates for Further Scientific Review as Potential Occupational Carcinogens" (53). It should be noted, however, that a number of government agencies have established guidelines for the general handling of known or suspected carcinogens. The National Cancer Institute (54), the National Institutes for Health (55) and NIOSH (56) have recommended guidelines for carcinogenic substances which emphasize containment of the agent by engineering controls combined with the use of personal protective

equipment in designated areas to reduce exposures to the lowest feasible limit.

In view of the fact that chemotherapeutic agents will continue to be widely used, together with the need both to maintain aseptic conditions during drug preparation and handling and to protect the employee, special consideration should be given to the need for biological safety cabinets in which drugs are prepared and to work practices during handling outside the cabinet. In a survey of 21 NCI Comprehensive Cancer Centers (57), only 3 of the 21 used vertical laminar flow cabinets for containment of chemotherapeutic agents; the majority of centers used horizontal laminar flow hoods. The current (1981) guidelines for environmental control in hospital pharmacies from the Centers for Disease Control (58) address only the issue of nosocomial infections and thus recommend only horizontal laminar flow hoods for parenteral drug preparation. Thus, there is an urgent need to review the guidelines recommended to date together with the operating characteristics of available containment devices in order to develop a comprehensive set of guidelines for the handling of these agents.

References

1. Ames, B.N., McCann, J. and Yamasaki, E. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat Res 1975; 35: 347

2. McCann, J., Choi, E., Yamasaki, E. and Ames, B.N. Detection of carcinogens as mutagens in the Salmonella/microsome test: assay of 300 chemicals I. Proc Nat Acad Sci USA 1975; 72: 5135-5139

3. McCann, J. and Ames, B.N. Detection of carcinogens as mutagens in the Salmonella /microsome test: assay of 300 chemicals; discussion Part 2. Proc Nat Acad Sci USA 1976; 73: 950-954

4. Rinkus, S.J. and Legator, M.S. Chemical characterization of 465 known or suspected carcinogens and their correlation with mutagenic activity in the Salmonella typhimurium system. Cancer Res 1979; 39: 3289-3318

5. Purchase, I.F.H., Longstaff, E., Ashby, J., Styles, J.A., Anderson, P.A and Westwood, F.R. Evaluation of six short-term tests for detecting organic chemial carcinogens and recommendations for their use. Nature 1976; 264: 624-627

6. Devoret, R. Bacterial tests for potential carcinogens. Sci Am 1979; 241: 40-49

7. Karnofsky, D.A. and Clarkson, B.D. Cellular effects of anticancer drugs. Ann Rev Pharmacol 1963; 3: 337-428

8. Harris, C.C. The carcinogenicity of anti-tumor drugs: a hazard in man. Cancer 1976; 37: 1014

9. Painter, R.B. Inhibition of DNA replicon initiation by 4 nitroquinoline 1 oxide adriamycin and ethyleneimine. Cancer Res 1978; 38: 4445-9

10. Yang, R.C., Ozols, R.F. and Myers, C.E. The anthracycline antineoplastic drugs. N Engl J. Med 1981; 305: 139-153

11. Benedict, W.F., Baker, M.S., Harown, L., Choi, E., and Ames, B.N. Mutagenicity of cancer chemotherapeutic agents in the Salmonella/microsome test. Cancer Res 1977; 37: 2209-2213

12. Seino, Y., Nagao, M., Yahagi, T., et al. Mutagenicity of several classes of anti-tumor agents to Salmonella typhimurium TA 98, TA 100, and TA 92. Cancer Res 1978; 38: 2148-56

13. Harrison, B.R. Developing guidelines for working with antineoplastic drugs. Am J Hosp Pharm 1981; 38: 1686-1693

14. Haddow, A., Harris, R.J.C., Kon, G.A.R. and Roe, E.M.F. The growth inhibitory and carcinogenic properties of 4-aminostilbene and derivatives. Phil Trans Roy Soc London Ser A 1948; 241-247

15. Sternberg, S.S., Philips, F.S., and Cronin, A.P. Renal tumors and other lesions in rats following a single intravenous injection of daunomycin. Cancer Res 1972; 32: 1029-1036

16. Philips, F.S., Gilladoga, A., Marguardt, H. Sternberg, S.S. and Vidal, R.R. Some observations on the toxicity of adriamycin. Cancer Chemother Rep 1975; 6:177-181

17. Marquardt, H., Philips, F.S. and Sternberg, S.S. Tumorigenicity in vivo and induction of malignant transformation and mutagenesis in cell cultures by adriamycin and daunomycin. Cancer Res 1976; 36: 2065-2069

18. Weisburger, J.H., Griswold, D.P., Preejcan, J.D., Casey, H.E., Wood, H.B. and Weisburger, E.K. The carcinogenic properties of some of the principal drugs used in clinical cancer chemotherapy. Recent Results in Cancer Res 1975; 52: 1-17

19. Schmahl, D. and Habs, M. Experimental carcinogenesis of anti-tumor drugs. Cancer Treat Rev 1978; 5: 175-184

20. Harris, C.C. A delayed complication of cancer therapy-cancer. J Natl Cancer Inst 1979; 63: 275-277

21. Sieber, S.M. Cancer chemotherapeutic agents and carcinogenesis. Cancer Chemother Rep 1975; 59: 915-918

22. Sieber, S.M. and Adamson, R.H. Toxicity of antineoplastic agents in man: chromosomal aberrations, antifertility effects, congenital malformations and carcinogenic potential. Adv Cancer Res 1975; 22: 57

23. Rosner, F. Acute leukemia as a delayed consequence of cancer chemotherapy. Cancer 1976; 37: 1033-1036

24. Wall, R. and Clausen, K. Carcinoma of the urinary bladder in patients receiving cyclophosphamide. N Engl J Med 1975; 293: 271-273

25. Thielde, T. and Christensen, B.C. Bladder tumors induced by chlornaphazin. Acta Med Scand 1969; 185: 133-137

26. Perlman, M. and Walker, R. Acute leukemia following cytotoxic chemotherapy (letter). J Am Med Assoc 1973; 224: 250

27. Little, J.B. Relationship between DNA repair capacity and cellular aging. Gerontology 1976; 22: 28-55

28. Benditt, E.P. The origin of atherosclerosis. Sci Am 1977; 236: 74-84

29. Devita, V.T. Jr. Principles of chemotherapy. In "Cancer, principles and practice of oncology." Eds. Devita, V.T. Jr., Hellman, S. and Rosenberg, S. Philadelphia, J.B. Lippincott, 1982.

30. Yamasaki, E. and Ames, B.N. Concentration of mutagens from urine by absorption with the nonpolar resin XAD-2: cigarette smokers have mutagenic urine. Proc Natl Acad Sci USA 1977; 74: 3555-3559

31. Von Doorn, R., Bos, R.P., Leijdekkers, C.M., Wagenaas-Zegers, M.A.P., Theuws, J.L.G., and Henderson, P.T. Thioether concentration and mutagenicity of urine from cigarette smokers. Int Arch Occup Environ Health 1979; 43: 159-166

32. Kurvink, K., Bloomfield, C.D., Keenan, K.M. et al. Sister chromatid exchanges in lymphocyte cultures from patients with malignant lymphoma. Human Genet 1978; 44: 137-144

33. Schinzel, A. and Schmid, W. Lymphocyte chromosome studies in humans exposed to chemical mutagens. The validity of the method in 67 patients under cytostatic therapy. Mutat Res 1976; 40: 139-166

34. Lambert, B., Ringborg, V. Herpes, E. and Lindglad, A. Sister chromatid exchanges in lymphocyte cultures of patients receiving chemotherapy for malignant disorders. Cancer Treat Rep 1978; 62: 1413-1419

35. Waksvik, H., Brogger, A. and Klepp, O., Chromosome analyses of nurses handling cytostatic agents. Cancer Treat Rep 1981; 65: 607-610

36. Norppa, H., Sorsa, M., Vainio, H., Grohn, P., Heinonen, E., Holsh, L., and Nordman, E. Increased sister chromatid exchange frequencies in lymphocytes of nurses handling cytostatic drugs. Scan J Work Environ Health 1980; 6: 299-301

37. Siebert, D. and Simon, U. Cyclophosphamide: pilot study of genetically active metabolites in the urine of a treated human patient. Mutat Res 1973; 19: 65-72

38. Minnich, V., Smith, M.E., Thompson, O.T., Kornfeld, S., and Holsti, L.R. Detection of mutagenic activity in human urine using strains of S. typhimurium. Cancer 1976; 38: 1253-1258

39. Falck, K., Grohn, P., Sorsa, M., Vainio, H., Hemonen, E., Holsti, L.R. Mutagenicity in urine of nurses handling cytostatic drugs. Lancet 1979; (i) 1250

40. Staiano, N., Gallelli, J.F., Adamson, R.H. and Thorgeirsson, S.S. Lack of mutagenic activity in urine from hospital pharmacists admixing antitumor drugs. (Letter) Lancet 1981; (ii) 615-616

41. Wilson, J.P., and Solimando, D.A. Anti-neoplastics-a safety hazard (Letter) Am J Hosp Pharm 1981; 38: 624

42. Nguyen, T.V., Theiss, J.C. and Matney, T.S. Exposure of pharmacy personnel to mutagenic antineoplastic drugs. Cancer Res 1982; 42: 4792-4796

43. Hoffman, D.M. (Editorial) Chemotherapy should be handled with care. Oncology Times 1980; 2: 2

44. Hoffman, D.M. The handling of antineoplastic drugs in a major cancer center. Hosp Pharm 1980; 15: 302-305

45. Zimmerman, P.F., Larsen, R.K., Barkley, E.W., and Gallelli, J.F. Recommendations for the safe handling of injectable antineoplastic drug products. Am J Hosp Pharm 1981; 38: 1693-1695

46. National Institutes of Health. Recommendations for the safe handling of parenteral anti-neoplastic drugs. NIH Division of Safety. PHS DHHS 1982.

47. The Society of Hospital Pharmacists of Australia. Guidelines for safe handling of cytotoxic drugs in pharmacy departments and hospital wards. 1980. (Specialty Practice Committee on Parenteral Services).

48. Canadian Society of Hospital Pharmacists. Guidelines for the handling of hazardous pharmaceuticals. Canad J Hosp Pharm 1981; 34: 126-128

49. Stolar, M.H. Guidelines for handling cytostatic drugs in hospitals. Am J Hosp Pharm 1983; 40: 1163-1171

50. National Institutes of Health. Laboratory Safety Monograph. A supplement to the NIH guidelines for recombinant DNA research. NIH PHS DHEW 1979.

51. Stuart, D.G., First, M.W., Jones, R.L., and Eagleson, J.M. Comparison of chemical vapor-handling by three types of biological safety cabinets. 1983; P and M C Forum 21-24. March/April.

52. Reynolds, R.D., Ignoffer, R., Lawrence, J., Torti, F.M., Koretz, M., Anson, N. and Meier, A. Adverse reactions to AMSA in medical personnel. J Amer Med Assoc 1982; 66: 1885

53. Occupational Safety and Health Administration. List of substances which may be candidates for further scientific review and possible identification, classication and regulation as potential occupational carcinogens. Fed Register 1980; 45: 53672-9

54. National Cancer Institute. Safety standards for research including chemical carcinogens. 1975; NIH Pub. No. 76-900

55. National Institutes for Health. NIH Guidelines for the laboratory use of carcinogens. 1981; NIH Pub. No. 81-2385

56. National Institute for Occupational Safety and Health. Carcinogens: regulation and control. 1977; US DHHS (NIOSH) Pub. No. 77-205

57. Tortorici, M. Precautions followed by personnel involved with the preparation of parenteral anti-neoplastic medications. Hosp Pharm 1980; 15: 295-301

58. Centers for Disease Control. Guidelines for the prevention and control of nosocomial infections. 1981; CDC Guidelines for Hospital Environmental Control: Pharmacy. October 1981; Office for Biosafety. Atlanta.

TABLE 1

Cancer chemotherapeutic agents in regular use at

Memorial Sloan Kettering Cancer Center, N.Y.C.

Adriamycin

Bleomycin

Cytoxan

Oncovin

Fluorouracil

TABLE 2

Job Title	Exposed	Control
Nurses	10	15
harmacist	7	5
Pharmacy technician	4	3
Total	21	23

Plus 1 chemotherapy and 1 control patient.

Sampling was carried out between February 18 and 21, 1981.

TABLE 4

Number of Revertant Colonies of Salmonella Typhimurium TA 98 & TA 100 by 3 Exposure Groups

		EXPOSED			NON-EXPOSED		
		n *	M	S.D.	n	M	S.D.
TA 98 Revertants							
per 300 ug. filter-sterilized urine	Nurses	10	46.6	12.1	15	47.9	17.2
	Pharmacists	7	42.0	12.9	5	45.2	13.3
	Pharm. Tech.	4	58.5	15.1	3	50.3	16.0
	TOTAL	21	47.3	13.6	23	47.6	15.7
per mg creatinine (50 ug urine extract per plate)	Nurses	9	2.8	2.6	15	4.6	6.2
	Pharmacists	7	2.8	3.5	5	3.6	5.1
	Pharm. Tech.	4	1.6	1.2	3	0.9	0.4
TOTAL		20	2.6	2.7	21	3.9	5.5
TA 100 Revertants							
per 300 ug. filter-sterilized urine	Nurses	10	256.1	58.5	15	248.0	99.0
	Pharmacist	7	239.9	62.8	5	274.8	73.2
	Pharm. Tech.	4	343.8	152.1	3	271.3	76.8
	TOTAL	21	267.4	87.7	23	256.9	88.9
per mg creatinine (50 ug urine extract per plate)	Nurse	9	1.7	2.3	15	3.3	3.4
	Pharmicists	7	4.4	8.2	5	1.4	2.0
	Pharm. Tech.	4	0.9	1.7	3	6.7	14.1
	TOTAL	20	2.5	5.1	23	3.3	5.4
CREATININE DETERMINATION							
mg creatinine/ 50 ug urine extract	Nurse	10	13.1	7.4	15	14.3	9.7
	Pharmacists	7	14.7	9.5	5	18.4	9.4
	Pharm. Tech.	4	23.0	14.9	3	14.2	13.5
	TOTAL	21	15.5	10.0	23	15.2	9.7

DMSO = dimethyl sulfoxide AAF = 2-acetyl aminofluorene
Mean control (Solvent) Values:
TA 100+DMSO: 146 $\pm$ 19.4; TA 98 + DMSO: 27 $\pm$ 4.71;
TA 100+50 ug AAF: 1974 $\pm$ 555; TA 100+25 ug. AAF: 540 $\pm$ 52.7;
TA 98 + 50 ug AAF 6351 $\pm$ 845.8; TA 98+25ug AAF; 1695 $\pm$ 329.6

* In this Table and the Tables that follow, n = the numbers of subjects for which assays were performed; these may not always equal the original number of subjects where a determination could not be made.

TABLE 5

Salmonella typhimurium
Number of Revertant Colonies of TA 98 and TA 100 by Smoking Group

	Current Smokers			Non or Ex Smokers		
TA 98 Revertants	n	M	SD	n	M	SD
per 300 ug. filter sterilized urine	15	51.2	16.8	29	45.6	13.2
per mg creatinine (50 ug urine extract per plate)	14	6.2	6.7	29	1.8	1.5
TA 100 revertants.						
per 300 ug. filter-sterilized urine	15	257.1	92.7	29	267.5	85.7
per mg creatinine (50 ug urine extract per plate)	14	4.1	6.2	29	2.4	4.7
mg creatinine (50 ug per urine extract per plate)	15	14.2	9.7	29	15.9	9.9

TABLE 6

Toxicity of urine % survival of colonies at 50 ug and 150 ug urine extract/plate by exposure group.

		Exposed			Non-Exposed		
		n	M	SD	n	M	SD
TA 98: % survival at 50 ug urine extract/ plate	Nurses	5	94.9	5.4	8	96.7	12.8
	Pharmacists	3	92.1	9.1	2	99.0	9.9
	Pharm. Tech.	1	90.7	-	2	95.8	5.4
	TOTAL	9	93.5	6.2	12	97.0	10.8
TA 100: % survival at 50 ug urine extract/ plate	Nurses	5	96.0	7.5	8	100.6	6.5
	Pharmacists	3	92.3	8.7	2	98.4	9.3
	Pharm. Tech.	1	56.1	-	2	103.4	5.1
	TOTAL	9	80.3	14.7	12	100.7	6.3
TA 100: % survival at 150 ug urine extract/ plate	Nurses	6	90.0	51.5	10	92.1	37.9
	Pharmacists	4	94.6	25.3	3	49.2	33.2
	Pharm. Tech.	3	38.7	48.1	2	121.9	34.1
	TOTAL	12	79.6	46.9	15	87.5	40.8

TABLE 7

Toxicity of urine: % survival of colonies at 50 ug and 150 ug urine extract/plate by smoking group

	Current Smokers			Non or Ex-Smokers		
	n	M	S.D	n	M	S.D.
TA 98: % survival at 50 ug urine extract/plate	8	93.4	8.5	13	96.7	9.5
TA 100: % survival at 50 ug	8	95.7	17.4	13	96.6	7.0
TA 100: % survival at 150 ug	10	88.3	45.5	18	81.3	42.8

TABLE 8

Urine mutagenicity: results of analysis of variance *

Variable	Exposure Group		Job Title		Interaction of Exposure & job title		Smoking Group	
	F	p	F	p	F	P	F	P
TA 98 revertants per 300 ug filter sterilized urine	0.02	0.89	0.98	0.39	0.32	0.73	0.99	0.33
TA 98 revertants per mg creatinine for 50 ug urine extract/plate	0.52	0.47	1.36	0.27	0.13	0.88	12.56	0.01
TA 100 revertants per mg creatinine for 50 ug urine extract/plate	0.32	0.57	1.14	0.33	0.82	0.45	0.59	0.45
TA 100 revertants per 300 ug filter sterilized urine	0.77	0.39	0.13	0.88	1.59	0.22	1.16	0.29
TA 98; % survival colonies at 50 ug urine extract/plate	0.44	0.52	0.03	0.97	0.07	0.93	0.27	0.61
TA 100; % survival colonies at 50 ug urine extract/plate	27.65	0.01	8.57	0.01	11.19	0.01	1.9	0.19
TA 100; % survival colonies at 150 ug urine extract/plate	0.50	0.48	0.54	0.59	3.34	0.06	0.02	0.88
mg creatinine per 50 ug urine extract	0.18	0.67	0.76	0.48	0.94	0.4	0.35	0.56
number years worked at hospital	1.17	0.29	1.46	0.25	1.13	0.33	1.06	0.31
Number years prepared handled/administered cancer chemotherapeutic agents	7.22	0.01	0.26	0.77	0.19	0.83	0.44	0.51
Age 1.17	0.29	1.46	0.25	1.13	0.33	1.06	0.31	

* Number of subjects for whom data available for each variable as in Tables 4 - 7.

TABLE 9

Number of individuals with positive urine mutagenicity *
by exposure group and smoking status.

Exposure Group	n		No + ve TA 98		No + ve TA 100	
	Sm	Ex/non Sm	Sm	Ex/non Sm	Sm	Ex/non sm
Exposed						
Nurses	3	7	1	0	0	0
Pharmacists	5	2	0	1	0	0
Pharmacy Technicians	2	2	0	1	0	1
Controls						
Nurses	5	10	2	1	1	0
Pharmacists	1	4	0	0	0	1
Pharmacy Technicians	2	1	0	0	0	0

* An individual result is considered positive if the number of revertants on the test plate is 2.5 times or greater the mean number of revertants for the DMSO solvent control plates.

TABLE 10

No TA 98 & TA 100 revertant colonies/plate for 300 ug filter-sterilized urine by exposure group and job title

Job Title	exposed			non-exposed		
	n	TA 98	TA 100	n	TA 98	TA 100
Nurses	10	46.6	256.1	15	47.9	248.0
Pharmacists & Technicians	11	48.0	277.6	8	47.1	273.5

No. TA 98 & TA 100 revertant colonies/plate & 50 ug urine extract by exposure group & job title.

Job Title	exposed			non-exposed		
	n	TA 98	TA 100	n	TA 98	TA 100
Nurses	9	2.8	1.72	15	4.6	.3
Pharmacists & Technicians	11	2.4	3.1	8	2.6	3.1

TABLE 11

Number of TA 98 and TA 100 revertant colonies/plate for 50 ug urine extracts by exposure group, job title and smoking status

	n	TA 98 M + S.D.	TA 100 M + S.D.
Non-Smokers			
Exposed nurses	7	47 ± 7**	178 ± 24*
Exposed pharmacists & technicians	7	42 ± 14**	166 ± 23
Unexposed nurses	10	64 ± 45**	181 ± 46*
Unexposed pharmacists & technicians	5	44 ± 6**	157 ± 17
Smokers			
Exposed nurses	3	42 ± 38	163 ± 25
Exposed pharmacists & technicians	2	88 ± 63**	192 ± 7*
Unexposed nurses	5	158 ± 235*	215 ± 83*
Unexposed pharmacists & technicians	5	113 ± 131**	196 ± 56*
DMSO solvent controls	14	27 ± 6	148 ± 23

t test (2 sided) for significance compared to mean value for revertants of 14 DMSO control plates: * = p = less than 0.05 ** = P = less than 0.01
Control plates:
DMSO TA 98: 27 ± 6
DMSO TA 100: 148 ± 23

Appendix A

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
CINCINNATI, OHIO 45226

EP 80:41
AGREEMENT TO PARTICIPATE IN MEDICAL STUDY

I, _____, age _____
(Print Name)

agree to participate in a medical study of employees of Memorial Sloan-Kettering Hospital Chemotherapy and Pharmacy Departments. This study is being conducted by personnel from the National Institute for Occupational Safety and Health (NIOSH). The purpose of this study is to determine whether there are mutagenic effects in the urine possibly resulting from exposure from working with cancer drugs and/or other substances.

In addition to answering questions about my health I understand that the medical study will include a urine test. I understand that urine samples will involve collecting my urine over a specified period of time on ~~two different~~ one day. However, the risk of any more serious injury or other effect on my health is negligible.

I understand that my participation in this study is voluntary and that I may withdraw from the study at any time. I understand that NIOSH will notify me of my test results, and that these results as well as all medical and other personal information will be considered confidential in accordance with the Privacy Act of 1974 (Public Law 93-579). I understand that, except for diseases reportable to public health authorities or other disclosures of information required by law or court order, this information will not be given to anyone else unless I so authorize in writing.

I understand that in the unlikely event of physical injury resulting from the medical procedures, NIOSH will only be able to provide emergency treatment. Any compensation for medical care or lost wages will have to be obtained under the Federal Tort Claims act [82 USC 1346(b)].

All questions concerning my participation in this study have been answered to my satisfaction. Future inquiries may be directed to William Halperin, M.D. or Arthur Watanabe, Pharm.D., Hazard Evaluations and Technical Assistance Branch, NIOSH, 4676 Columbia Parkway, Cincinnati, Ohio 45226, telephone 513-684-2732.

Signature _____ Date _____

Mailing Address _____

_____

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DISEASE CONTROL
U.S. PUBLIC HEALTH SERVICE
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

EP 80:41
Occupational Exposure to Cancer Chemotherapy Agents
Memorial Sloan-Kettering Cancer
New York, New York

Case ID _____:____

I. DEMOGRAPHIC

1. Name: _____

   Address: _____

   _____

   Telephone No. _____

2. Sex: Male _____ Female _____

3. Birth Date: _____

4. Race: Anglo _____ Black _____ Hispanic _____
   Asian _____ Other _____

II. MEDICAL

1. Do you have or have you had any chronic medical problems such as:

   a. High blood pressure
   b. Kidney disease
   c. Liver
   d. Cancer
   e. Other

   No _____ Yes _____ If yes, specify _____

2. Do you regularly take any medicines such as:

   a. Prescription drugs
   b. Non-prescription drugs
   c. Vitamins

   No _____ Yes _____ If yes, what _____

   Did you take any medications in the past 24 hours?

   No _____ Yes _____ If yes, what _____

3. Which of the following describes your smoking status?

   a. Never smoked _____
   b. Smoked, but quit _____
      If so, when? Month _____ Year _____
   c. Current smoker
      Average number of cigarettes/day _____
      Number of years _____
      Filtered: _____ Non-filtered: _____
   d. Cigar smoker _____
   e. Pipe smoker _____
   f. Chew tobacco _____

4. Did you smoke any materials today? No _____ Yes _____

   If yes, what _____

5. Which of the following do you regularly drink:

	No	Yes	If yes, how much/day
Coffee	___	___	_____
Tea	___	___	_____
Pop	___	___	_____
Diet sodapop	___	___	_____
Alcohol	___	___	_____

6. Did you consume any of the above beverages in past 24 hours?

   No _____ Yes _____ If yes, specify _____

7. Did you use saccharin or eat any saccharin containing candy, gum, or food in the past 24 hours?

   No _____ Yes _____ If yes, specify _____

III. WORK AND EXPOSURE HISTORY

1. What is your job title?

   a. Chemotherapy Nurse _____
   b. Pharmacist _____
   c. Pharmacy technician _____
   d. Floor Nurse _____
   e. Other _____
      Specify, _____

2. What shift hours did you work today?

   a. From _____ To _____

b. Are these your regular shift hours?

No _____ Yes _____

If No, what is your regular shift? _____

3. What days of the week do you usually have off?

a. Indicate which days: Sat Sun Mon Tue Wed Thu Fri

b. When were your most recent days off?

_____

4. Do you regularly prepare cancer chemotherapeutic drugs?

a. No _____ Yes _____

b. If yes, did you prepare cancer chemotherapy drugs:

1. Today	No _____	Yes _____
2. Yesterday	No _____	Yes _____
3. Day before yesterday?	No _____	Yes _____

5. Do you regularly ADMINISTER cancer chemotherapeutic drugs?

a. No _____ Yes _____

b. If yes, did you administer cancer chemotherapy drugs:

1. Today?	No _____	Yes _____
2. Yesterday?	No _____	Yes _____
3. Day before yesterday?	No _____	Yes _____

6. If you answered YES to either 4 or 5, what cancer chemotherapy drugs did you prepare or handle today?

_____

_____

_____

7. Today, did you take any of the following precautions when you prepared or administered cancer chemotherapy:

	Always	Sometimes	Never
a. Used Hood	_____	_____	_____
b. Wore gloves	_____	_____	_____
c. Wore fask mask	_____	_____	_____
d. Other, specify _____	_____	_____	_____

8. How long have you:

   a. Worked at this hospital? _____Years

   b. Prepared, handled or administered cancer chemotherapeutic drugs?

      _____Years