Preventing Bladder Cancer from Exposure to o-Toluidine and Aniline

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WARNING! Workers exposed to o-toluidine or aniline may be at increased risk for developing bladder cancer.

The National Institute for Occupational Safety and Health (NIOSH) requests assistance in preventing bladder cancer in workers exposed to o-toluidine and aniline, both of which have been shown to induce tumors in experimental animals. This Alert presents significant new epidemiologic evidence that clearly associates o-toluidine and aniline with an increased risk of bladder cancer.

NIOSH requests employers, editors of appropriate trade journals, and all those responsible for occupational safety and health to bring this information to the attention of workers potentially exposed to o-toluidine and aniline. NIOSH further requests that employers and workers implement the recommendations in this Alert to reduce exposures to the lowest feasible concentration.

Background

o-Toluidine and aniline are aromatic amines used as intermediates in the manufacture of a variety of dyes, pharmaceuticals, pesticides, and chemicals employed in the manufacture of rubber. Chronic exposures to o-toluidine and aniline have been implicated in previously reported cases of bladder cancer in workers, but always with concurrent exposures to other known bladder carcinogens [IARC 1982]. o-Toluidine is produced or used in the United States by 13 facilities, with onsite quantities ranging from 1,000 pounds to 10 million pounds. Aniline manufacture and use in the United States is reported by 62 facilities, with onsite quantities ranging from 100 pounds to 50 million pounds [NLM 1989].

NIOSH estimates that during the period 1981-83, 28,483 workers were potentially exposed to o-toluidine and 35,781 workers were potentially exposed to aniline [NIOSH 1983]. Primary routes of exposure to these compounds are inhalation and dermal contact.

Exposure Limits

The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for o-toluidine is 5 parts per million parts of air (5 ppm) as an 8-hour time-weighted average (TWA) exposure with a notation for skin absorption [29 CFR* 1910.1000]. The OSHA PEL for aniline is 2 ppm as an 8-hour TWA with a notation for skin absorption.

On the basis of reviews of human and animal data in the literature and the significant new epidemiologic evidence of increased bladder cancer presented in this Alert, NIOSH concludes that o-toluidine and aniline are potential occupational carcinogens as defined in the OSHA carcinogen policy [29 CFR 1990]. NIOSH therefore recommends reducing exposures to the lowest feasible concentration.

The American Conference of Governmental Industrial Hygienists (ACGIH) has identified o-toluidine as a suspected human carcinogen and has established a threshold limit value (TLV®) of 2 ppm as an 8-hour TWA with a

skin notation [ACGIH 1990]. The ACGIH TLV for aniline is 2 ppm as an 8-hour TWA with a skin notation.

Published Studies of Carcinogenic Effects

As summarized in the following review, both o-toluidine and aniline have produced tumors in animals. However, o-toluidine produced a greater number and variety of tumors at lower doses than did aniline. NIOSH therefore considers the evidence of carcinogenicity stronger for o-toluidine than for aniline. However, because aniline did produce tumors in one rat bioassay study, aniline must also be regarded as potentially carcinogenic in humans.

Studies in Animals

The carcinogenicity of the hydrochloride salt of o-toluidine (o-toluidine HCl) was demonstrated in three chronic feeding studies in rats and mice [NCI 1979a; Weisburger et al. 1978; Hecht et al. 1982]. The use of the hydrochloride salt rather than o-toluidine in these studies is considered to be of little consequence because o-toluidine will react with stomach acid to form the hydrochloride salt [EPA 1984]. Tumors were induced in various organs, including the skin, subcutaneous tissue, mammary glands, urinary bladder, liver, spleen, peritoneum, and abdominal viscera.

Some evidence exists for the carcinogenicity of aniline hydrochloride salt (aniline HCl) in rats [NCI 1978; Hagiwara et al. 1980; White et al. 1948].

The carcinogenicity of aniline and o-toluidine in experimental animals can be compared in studies conducted under similar conditions [NCI 1978; NCI 1979a]. In the assays of aniline HCl in mice, no statistically significant increases in the number of tumors were noted for any site in the exposed animals compared with the controls. However, lower doses of o-toluidine HCl in mice produced a significant increase of hepatocellular carcinomas and adenomas in females and hemangiosarcomas in males. In rats, aniline HCl produced an excess of fibromas or sarcomas in both males and females and an excess of hemangiosarcomas in males. The same doses of o-toluidine HCl

in rats produced a greater number and variety of tumors, including transitional cell carcinomas and papillomas of the bladder in females.

Studies in Humans

Case et al. [1954]

The epidemiologic data available for both chemicals are extremely limited. In a large study of bladder cancer in British dyestuff workers, Case et al. [1954] found no evidence that workers exposed to aniline alone had an increased risk of bladder tumors. However, this finding was based on only one observed death and is not conclusive. No other epidemiologic studies of aniline alone are available.

Rubino et al. [1982]

Rubino et al. [1982] reported a 62-fold increase in bladder cancer mortality (5 cases observed versus 0.08 expected) among a group of workers exposed to o-toluidine and 4,4'-methylenebis (2-methylaniline) in an Italian dyestuff factory. 4,4'-Methylenebis-(2-methylaniline) has been identified as an animal carcinogen [Stula et al. 1975].

Stasik [1988]

Stasik [1988] reported a 72-fold increase (8 cases observed versus 0.11 expected) of bladder cancer among 116 workers involved in the manufacture of 4-chloro-o-toluidine between 1929 and 1970. o-Toluidine was also present at this plant, but exposure to 4-chloro-o-toluidine, a carcinogen in mice [Weisburger et al. 1978; NCI 1979b], was thought to be more extensive.

Summary Reviews

IARC [1982]

The International Agency for Research on Cancer (IARC) has cited several reports regarding o-toluidine and aniline [IARC 1982]. However, these

studies either included workers with exposure to known bladder carcinogens, or they were not reported in sufficient detail to draw conclusions about the carcinogenicity of o-toluidine and aniline. IARC concluded that “there is limited evidence for the carcinogenicity of aniline hydrochloride in experimental animals. The available epidemiologic data are insufficient to allow a conclusion as to the carcinogenicity of aniline.” IARC also concluded that “there is sufficient evidence for the carcinogenicity of o-toluidine hydrochloride in experimental animals. An increased incidence of bladder cancer has been observed in workers exposed to o-toluidine, but as all were exposed to other possible carcinogenic chemicals, o-toluidine cannot be identified specifically as the responsible agent. o-Toluidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.” The IARC classification of these chemicals remained the same in 1987 [IARC 1987].

NTP [1989a]

The National Toxicology Program (NTP) identifies o-toluidine and o-toluidine hydrochloride in its listing of “substances which . . . may reasonably be anticipated to be carcinogens” [NTP 1989a].

NIOSH Study of Carcinogenic Effects

Background

In December 1989, NIOSH completed a study of bladder cancer incidence at a plant that had used o-toluidine and aniline since 1957 to manufacture a rubber antioxidant [NIOSH 1989]. Aniline had also been used to manufacture a rubber accelerator since 1970. The union requested this investigation because eight cases of bladder cancer had been reported between 1973 and 1988 among workers in the department where there was a potential for exposure to o-toluidine and aniline. Other chemicals were used in the manufacturing processes, but only o-toluidine, aniline, and hydroquinone have been evaluated as potential carcinogens by IARC, and only o-toluidine has been classified as an animal carcinogen and “possibly carcinogenic to

humans" [IARC 1987]. As a result of the IARC review of data for aniline and hydroquinone, both were labeled as "not classifiable as to carcinogenicity in humans" [IARC 1987].

The NTP recently reported the results of a 2-year bioassay of hydroquinone [NTP 1989b]. "Some evidence" of carcinogenicity was found in male and female rats, and in female mice. "No evidence" of carcinogenicity was found in male mice. Nonmalignant proliferative lesions were considered "possible precursors in the development of hepatocellular neoplasia." NIOSH did not evaluate exposures to hydroquinone, but company data indicate historical exposures below the OSHA PEL of 2 mg/m^3.

NIOSH also investigated the possibility of exposure to 4-aminobiphenyl, a known human bladder carcinogen formed by dimerization of aniline [Melnick et al. 1971]. 4-Aminobiphenyl is regulated by OSHA as an occupational carcinogen [29 CFR 1910.1011]. Investigators took bulk samples of the starting products, five intermediates, and the final products. Trace amounts of 4-aminobiphenyl (much less than 1 ppm) were found in samples of aniline and o-toluidine taken from the tank cars as they arrived from the manufacturer, and from the feedstock for the reactor in which the rubber accelerator was formed. The chemistry of the process makes it likely that the amount of 4-aminobiphenyl formed would be small. In addition, it is likely that 4-aminobiphenyl present in the starting materials was consumed by the process reactions.

Procedures

Information was collected about the history of the processes in which o-toluidine or aniline was used, area air samples were collected, and process operations were observed. Industrial hygiene sampling data collected by the company were reviewed.

All air concentrations of o-toluidine and aniline measured by NIOSH were below 1 ppm, a concentration consistent with company data available since 1975. Workers occasionally came into contact with liquid processing chemicals (including o-toluidine and aniline), with portions of their cotton

work clothes becoming soaked with the liquid. Consequently, some workers had prolonged skin contact and the potential for skin absorption.

Because workers were exposed to both o-toluidine and aniline, it was not possible to separate the health effects of exposures to these chemicals.

Dermal absorption of o-toluidine and aniline may be a significant route of exposure, and air measurements therefore may not reflect worker exposure. Ongoing investigations at this plant will include an extensive survey of current exposures. This survey will use measurements of urinary o-toluidine and aniline (or their metabolites) to assess total exposure.

After carefully reviewing the processes and job categories at the plant, NIOSH investigators concluded that any worker assigned to the department that used o-toluidine and aniline should be considered “definitely exposed” to these chemicals. If workers had ever been assigned to the maintenance, janitorial/yard, or shipping departments, they were considered “possibly exposed.” All other workers were considered “probably unexposed.”

Employment records were used to identify all individuals who had ever worked at the plant. Cases of bladder cancer were identified from records of the company, the union, and the State cancer registry. Cases identified from company and union records were confirmed by requesting medical records. The number of bladder cancers observed among company workers was compared with the number expected on the basis of incidence rates in New York State using the NIOSH lifetable program [Waxweiler et al. 1983]. These rates were specific for age, sex, and calendar time (5-year intervals). The observed and expected cases were recorded only for the period 1973 though 1988 because the State cancer registry records were thought to be relatively complete during that time.

Results

Results of the study (Figure 1) illustrate the association of bladder cancer in workers with exposure to o-toluidine and aniline. Among the 1,749 individuals who were ever employed at the plant, 13 cases of bladder cancer

were observed, whereas 3.61 cases were expected on the basis of New York State incidence rates. The ratio of observed to expected cases (also known as the standardized incidence ratio, or SIR) was 3.60,** a ratio that is highly significant (P***,**** = 0.0001) and is therefore very unlikely to have occurred by chance. Among 708 workers considered “definitely exposed” to o-toluidine and aniline, 7 cases of bladder cancer were observed and 1.08 cases were expected (SIR = 6.48, P**** = 0.0001). Among 288 workers who were “possibly exposed” to o-toluidine and aniline, 4 cases of bladder cancer were observed and 1.09 were expected (SIR = 3.66, P**** = 0.03). The SIR was elevated among 753 workers who were “probably unexposed,” but it was not significantly different from 1.00 (SIR = 1.39, P = 0.42).

NIOSH investigators took into account the possible role of smoking in producing the excess incidence of bladder cancer among workers exposed to o-toluidine and aniline. However, smoking without occupational exposure to o-toluidine and aniline would account for less than a twofold increase in bladder cancer [NIOSH 1989] compared with the greater than six-fold increase observed among workers definitely exposed to o-toluidine and aniline.

Among definitely exposed workers employed in the area of the plant where o-toluidine and aniline were used, the bladder cancer risk increased with duration of work in the area. No cases were observed among workers employed in the area for fewer than 5 years. Among workers employed in the area for 5 to 10 years, 1 case was observed and 0.11 was expected (SIR = 8.79, P = 0.11). Among workers employed in the area for 10 or more years, 6 cases were observed and 0.22 was expected (SIR = 27.2, P**** = 0.0000001).

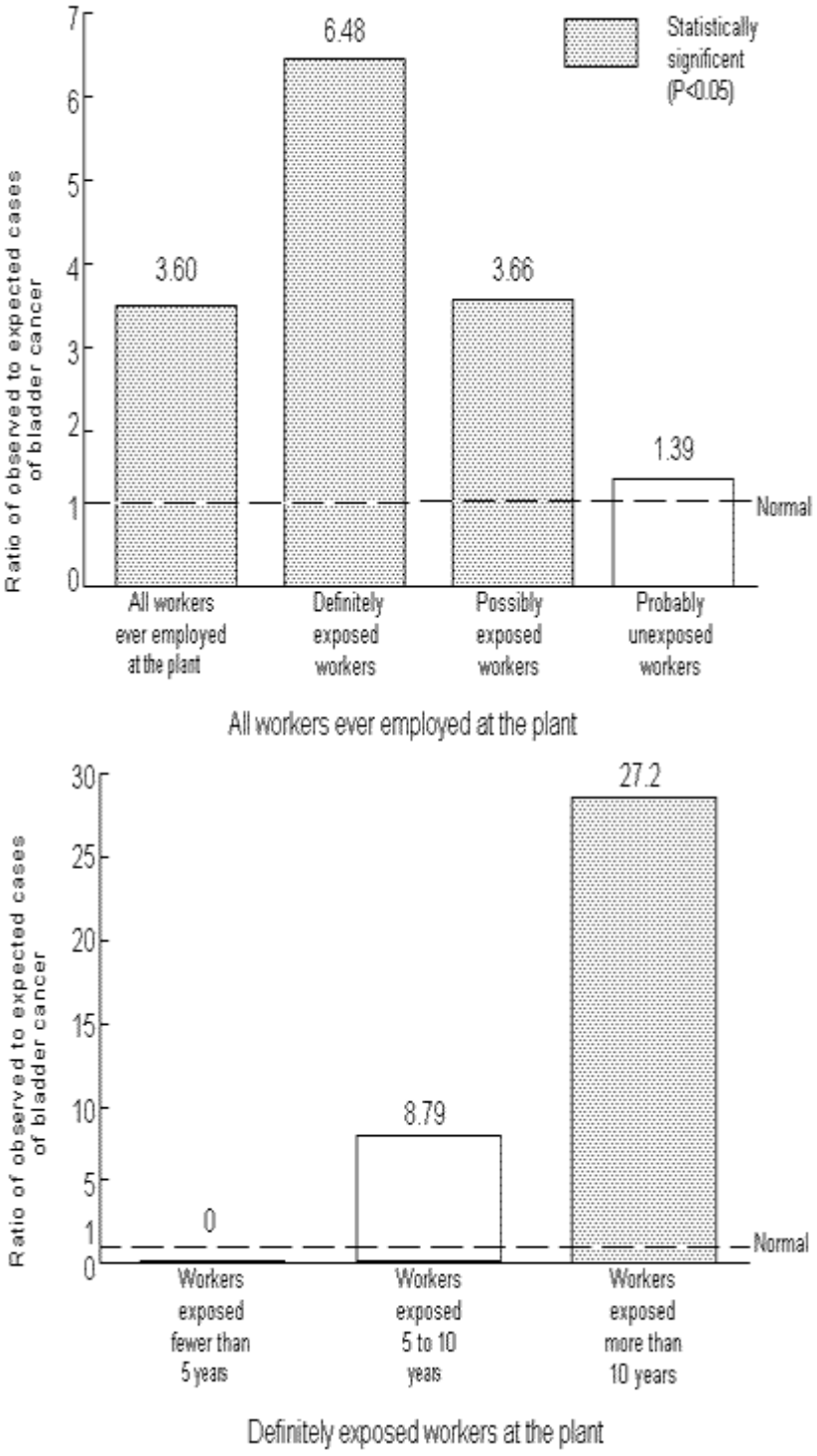

Figure 1. Incidence of bladder cancer among workers exposed to o-toluidine and aniline.

Conclusions

Epidemiologic evidence reported by NIOSH [1989] clearly associates occupational exposure to o-toluidine and aniline with an increased risk of bladder cancer among workers. The risk of bladder cancer at the plant was greatest among workers with possible and definite exposures to o-toluidine and aniline, and the risk increased with duration of exposure. The effects of o-toluidine and aniline could not be separated epidemiologically. However, NIOSH investigators concluded that because o-toluidine induces a greater number and variety of tumors in animals at lower doses than aniline, it is more likely to be responsible for the observed bladder cancers. The bladder cancer excess is not likely to be related to other chemicals present in the department, including hydroquinone and 4-aminobiphenyl.

Recommendations

On the basis of significant evidence of increased risk of bladder cancer in humans, NIOSH recommends the following measures to reduce exposures to o-toluidine and aniline to the lowest feasible concentrations. The potential for release of o-toluidine and aniline to the work environment and for contact of these chemicals with the workers' skin should be minimized through the use of the engineering controls, work practices, and personal protective equipment described in this section.

Hazard Awareness

Workers should be informed about the potential carcinogenic effects of o-toluidine and aniline. A copy of this Alert and material safety data sheets (MSDSs) should be given to any worker who may be exposed to o-toluidine or aniline. Warning signs (such as the one printed on the last page of this Alert) should be posted in areas where exposure to o-toluidine and aniline may occur. These signs should list exposure hazards and recommend protective measures.

Training

Training of workers should included information about the following items: (a) the possible carcinogenic effects of exposure, (b) the importance of

avoiding skin contact, (c) specific work practices, and (d) the use of appropriate protective equipment, including gloves and respiratory protection.

Engineering Controls

Engineering controls that should be considered by employers include (a) use of enclosed processes, (b) separation of the worker from the processes, and (c) design and installation of appropriate ventilation. Examples of engineering controls are as follows:

- The use of enclosed systems for unloading bulk chemicals. Such systems should be equipped with snap-lock or other types of transfer hose connections for quick hook-ups and disconnections. A purging system should be included to remove excess chemicals from the transfer hose before disconnection.
- The use of redundant controls such as double mechanical seals for process pumps and for other rotating or reciprocal equipment, or other types of back-up leak protection to prevent the release of chemical liquid or vapor to the work environment.
- The use of enclosed systems for sampling process liquids (e.g., lines and vessels with snap-lock fittings). The sampling ports should be equipped with a system to purge the port after sampling and before disconnection of the sampling vessel.

Work Practices

The following are examples of work practices that can be used to control exposures:

- The maintenance of good general housekeeping so that leaks and other process integrity problems can be readily detected and corrected.
- The use of clear labeling for all drums or containers in the work area that hold process chemicals. This labeling must conform with the requirements of the OSHA Hazard Communication Standard [29 CFR 1910.1200].

- The preventive maintenance of process equipment to prevent deterioration and subsequent development of leaks. This maintenance should include regular inspection of potential leak sites.
- The use of proper hygiene practices to minimize skin absorption (for example, proper use and removal of protective clothing, prohibition of eating and smoking in work areas, proper materials handling, etc.).

Personal Protective Equipment

Chemical Protective Clothing

To minimize skin contact and absorption, workers using o-toluidine and aniline should wear chemical protective clothing (CPC) such as gloves and aprons. Teflon® is the most protective material tested for o-toluidine. For aniline, the most protective materials (usually in the form of gloves) are butyl rubber, polyvinyl alcohol, Teflon, Saranex ®/Tyvek®, and polyethylene/ethylene vinyl alcohol (e.g., 4H ®, or SilverShield ®) [Forsberg and Mansdorf 1989]. Therefore, Teflon appears to be the most broadly protective material of those that have been tested against both o-toluidine and aniline. During short-duration tasks, Saranex/Tyvek clothing may be used to protect parts of the body other than the hands from o-toluidine and aniline.

The quality of the gloves made from these materials may vary significantly among glove producers [Mickelsen and Hall 1987]. Product-specific permeation data should therefore be obtained from the glove manufacturer.

If the potential exists for the spraying or splashing of liquids, workers should wear protective eyewear or faceshields.

Respiratory Protection

Although engineering controls and work practices should be used to minimize exposures to o-toluidine and aniline, respirators may be required in certain work situations–for example, when engineering controls or work practices are not technically feasible or during emergencies and maintenance

operations. The NIOSH recommendations for respiratory protection are based on the NIOSH position that both o-toluidine and aniline are potential occupational carcinogens.

Table 1 lists the types of respiratory protection recommended for various conditions of exposure to o-toluidine and aniline. For additional information about the selection and use of respirators, refer to the *NIOSH Respirator Decision Logic* [NIOSH 1987a] and the *NIOSH Guide to Industrial Respiratory Protection* [NIOSH 1987b]. Respirators should be approved by NIOSH and the Mine Safety and Health Administration (MSHA) [NIOSH 1990].

Table 1.–NIOSH recommended respiratory protection for workers exposed to o-toluidine or aniline

NIOSH recommended respiratory protection for workers exposed to o-toluidine or aniline

Condition	Minimum respiratory protection
Any measurable air concentration or emergency entry into environment containing unknown concentration	Any SAR* equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary SCBA** operated in a pressure-demand or other positive-pressure mode, or Any SCBA equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Firefighting	Any SCBA equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Escape only	Any air-purifying, full-facepiece canister respirator providing protection against organic vapors and equipped with an end-of-service-life indicator (ESLI), or Any SCBA equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode

* Supplied-air respirator.
[Return to top of table]
** Self-contained breathing apparatus.
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Environmental Monitoring

Periodic environmental monitoring [NIOSH 1984; 29 CFR 1910.1000] should be conducted using NIOSH or OSHA recommended methods to assess

exposures to workers and to help evaluate the effectiveness of engineering controls, work practices, and protective equipment.

Biological Monitoring

o-Toluidine and aniline may be inhaled, absorbed through the skin, or ingested. Thus biological monitoring may help detect exposure by any route. Specific recommendations for biological monitoring of o-toluidine and aniline cannot be made at this time, but results of ongoing NIOSH investigations of biological monitoring at the plant will be reported at a later date.

Medical Screening

Workers who have been exposed to o-toluidine or aniline should be notified that they may be at increased risk of bladder cancer and alerted to its signs and symptoms. These include (1) blood in the urine, (2) other changes in the appearance of the urine, (3) changes in urinary habits, (4) lumps in the groin or lower abdomen, and (5) pain in the lower abdomen or back.

Workers should be encouraged to see a doctor at once if they notice any of these symptoms. When bladder cancer symptoms are discussed with the worker, it is important to emphasize that the presence of these symptoms does not necessarily mean that the worker has bladder cancer.

Screening for bladder cancer has not been demonstrated to decrease disability and death from bladder cancer. However, a well designed study has never been done to evaluate these issues. NIOSH is currently reviewing its previous recommendations for cancer screening in general and for bladder cancer screening in particular. In the past, NIOSH has recommended that workers who have been exposed to potential bladder carcinogens be offered an annual urinalysis to include microscopic examination for microhematuria and cytologic examination for neoplastic cells. Recommendations about the frequency and types of screening tests for bladder cancer may vary in different plants. Until new recommendations are final, NIOSH continues to recommend that workers who have been exposed to potential bladder

carcinogens be offered an annual urine cytology and urinalysis for microhematuria either by dipstick or by microscopic examination.

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Notes

* Code of Federal Regulations. See CFR in references. [Return to body of text]

** The values for expected cases have been rounded to two decimal places; the SIRs calculated from these figures may be slightly different from the SIRs listed here. [Return to body of text]

*** The P value is the probability that the calculated SIR will occur by chance alone. [Return to body of text]

**** Statistically significant when P is less than 0.05. [Return to body of text]

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NIOSH ALERT

o-Toluidine/Aniline

WARNING!

Workers exposed to o-toluidine or aniline may have an increased risk of developing bladder cancer.

Take the following actions to protect yourself if you are exposed to o-toluidine or aniline:

- ***Be aware of the possible carcinogenic effects of exposure to o-toluidine and aniline.***
- ***Use the following engineering controls to reduce exposures to the lowest feasible concentrations:***
  - — Enclosed systems for unloading bulk chemicals
  - — Backup controls or other types of leak protection
  - — Enclosed systems for sampling process liquids
- ***Use the following good work practices to control exposures:***
  - — Maintenance of good general housekeeping
  - — Use of clear labeling for all containers of process chemicals
  - — Maintenance of process equipment to prevent deterioration and leaks
  - — Use of proper hygiene practices to minimize skin absorption:
    a. Proper use and removal of protective clothing
    b. Prohibition of eating and smoking in work areas
    c. Proper materials handling
- ***Cooperate with biological or environmental monitoring programs conducted by your employer.***
- ***Participate in medical screening programs offered by your employer.***

For additional information, see the NIOSH Alert on o-toluidine [DHHS (NIOSH) 90-116], or call 1-800-35-NIOSH. Single copies are available free from the following:

Publications Dissemination, DSDTT
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