# IV. ENVIRONMENTAL DATA

## Environmental Concentrations

The concentration of biphenyl amines in the air at the plant manufacturing o-tolidine around 1950 ranged from 2 to 87 μg/cu m and averaged about 20 μg/cu m [22], but specific o-tolidine levels were not given. Additional information on o-tolidine levels in the workplace environment was not found. However, environmental concentrations of o-tolidine for manufacturers and users can be only roughly estimated from current processing information. Because batch processing is used by both manufacturers and users, with the result that environmental levels of o-tolidine fluctuate from zero during off-production periods to a maximum when o-tolidine is produced or used, worker exposure to o-tolidine is expected to be intermittent, with the frequency of exposure depending on the frequency of production.

For manufacturing facilities, except for accidental spills or leaks, environmental levels would probably be highest near operating filter presses and driers. Bulk quantities of o-tolidine are also handled in dye manufacturing; 1,500-2,000 pounds are used for each batch operation. For these facilities, high levels can be expected when o-tolidine is weighed and when the reactor is being charged with o-tolidine. Other users of o-tolidine handle less than 200 pounds of o-tolidine per year in small quantities, generally milligrams [63]. It is expected that their exposure to airborne o-tolidine would be intermittent and possibly negligible.

o-Tolidine can enter the body by any route, particularly inhalation and skin contact [17,22]. A significant hazard comes from contaminated clothing [10,22,64]. Personal hygiene, removal of contaminated work clothing, separation of work clothing from street clothing, and showering at the end of the workshift have greatly reduced the absorption of o-tolidine [10,22].

## Control of Exposure

Inhalation and skin absorption of o-tolidine can be minimized by proper ventilation, cleaning operations not requiring direct exposure of workers, prompt cleanup and decontamination procedures using liberal amounts of water, employee education and attention to personal hygiene, and full-body protective equipment when necessary. In one case, a worker's urinary excretion of aminobiphenyl compounds was reduced 80% by attention to personal hygiene [22].

Proper ventilation is an important means of controlling respiratory exposure to o-tolidine and will help to minimize skin exposure by reducing the amount of o-tolidine available to settle out of the air. Guidelines for ventilation systems may be found in Industrial Ventilation--A Manual of Recommended Practice of the American Conference of Governmental Industrial

Hygienists (ACGIH) [65] and in Fundamentals Governing the Design and Operation of Local Exhaust Systems of the American National Standards Institute (ANSI) [66].

The most effective engineering control measure is enclosure of unit operations and processes. Closed systems are most effective if they are operated under negative pressure with respect to surrounding uncontaminated areas, and they are only effective if their integrity is maintained. This can be ensured by a program of periodic maintenance, especially of equipment parts, eg, gaskets and seals that are subject to wear, by frequent inspections for and immediate repair of leaks, and by the use of pressure-failure alarms in enclosures, hoods, and ductwork.

An alternative or supplement to closed processes is local exhaust ventilation used at all sources of o-tolidine emission. The hood should be as close to the emission source as possible and shaped to control the area of contamination. Airflow into the exhaust hood should be directed away from the worker, and the capture velocity of the exhaust hoods should be high enough to overcome opposing air currents and the kinetic velocity of generated dust particles within the working environment, including those caused by movements of the workers. A minimum airflow of 150 fpm is recommended, but final determination should be made by an industrial hygienist. An industrial hygiene survey should be performed to determine the proper hood design and capture velocity for the facility.

With the exception of o-tolidine manufacturers and dye makers, each user facility generally consumes less than 200 pounds/year. For these facilities, local exhaust ventilation in the form of a laboratory-type hood or glove box may be effectively used for batch operations in which o-tolidine is weighed, converted into a concentrated acid solution, or diluted; in repackaging operations; and in laboratory activities involving research or quality control. A properly designed and maintained laboratory hood or glove box can confine the area of contamination to the hood or glove box itself, thereby simplifying control procedures for preventing skin contact with and inhalation of o-tolidine. The hood or glove box should be located away from heavy traffic aisles, doorways, and supply grills. A minimum exhaust volume for the laboratory hoods of 150 cu ft/minute/sq ft (45 cu m/minute/sq m) of door area is recommended [65], but final determination should be made by an industrial hygienist. Hoods should be inspected monthly for the first 6 months and quarterly thereafter [65].

o-Tolidine is used in some batch operations as an intermediate in dye, pigment, and urethane production. Bulk quantities up to 1,500-2,000 pounds are weighed and then dumped into reactors to be chemically converted into the final product. In such operations, o-tolidine is generally handled for less than 1 hour. Dust emissions from the weighing operation should be controlled by the use of local exhaust ventilation. The hood should enclose as much of the scale as possible without interfering with the worker's performance.

Local exhaust ventilation can also be used to control dust in the charging or reaction vessels. However, an alternative approach is to operate the

reactor under negative pressure relative to the working environment. Negative pressure within the system should usually control a billowing effect that has been reported during the charging of reaction vessels in dye production [10].

Handling o-tolidine in the wet-cake or paste form provides additional safeguards by reducing the amount of dust liberated [10]. The liberation of dust may also be reduced by converting the o-tolidine base to its larger crystalline salt structure [10]. If possible, premeasured units of dry o-tolidine base or salts should be opened under water or other suitable liquid to reduce the amount of dust released when the package is opened.

## Environmental Sampling and Analytical Methods

### (a) Sampling

Because airborne o-tolidine is typically an aerosol, filters or impingers are most appropriate for personal air sampling, although no studies have been found on this point. Filters are effective for particulates. Glass-fiber filters are recommended to minimize pressure drop. They are clean, self-contained, and convenient. It is recommended that the filter be backed in series by silica gel to minimize losses from vaporization of the sample. This system of a filter backed by silica gel has been used successfully in sampling for benzidine [67] and other related biphenyl amines. Alternatively, impingers may be substituted for filters or filter and silica gel tandem devices for sampling. Hydrochloric acid [68] and distilled water [69] have been used as collecting media, but because recovery rates were not provided, their effectiveness in capturing o-tolidine cannot be evaluated. Because of the difficulties involved in obtaining breathing zone samples with impingers, filters are recommended to sample air in the breathing zone of workers. However, stationary impingers may be used for supplementary area sampling. Sampling with impingers should be avoided unless precautions are taken to prevent sample losses through foaming and solvent loss.

### (b) Analysis

Concentrations of airborne o-tolidine should be kept as low as possible to minimize worker exposure through both inhalation and skin absorption. The following discussion reviews several methods of analyzing o-tolidine and related compounds in air for environmental monitoring and in urine for biologic monitoring.

Matrka et al [70] described an oxidimetric (potentiometric) titration method for o-tolidine determination using cerium (IV) sulfate. Standards were prepared with 42-106 mg of o-tolidine dissolved in 45 ml of 0.1 N hydrochloric acid at 20 C. The indicator electrode was glossy platinum, the comparison electrode saturated calomel. The o-tolidine solution was titrated with 0.05 N cerium disulfate solution. The error between amounts of o-tolidine weighed and calculated after titration varied between 0.2% and 0.4%. Titration usually overestimated the actual amount. The authors mentioned other techniques of titration for o-tolidine, including titration with p-toluene sulfonic acid, but did not quantitatively compare those techniques with their

own. This oxidimetric method has a clearly marked end point but lacks specificity. The sensitivity of the method was not given, but this method probably is not sensitive at the microgram level.

Fluorometric [6,71,72] and colorimetic [68,69,73-76] methods have been developed for the analysis of biphenyl amines, including o-tolidine. The fluorometric techniques depend on the property of aromatic amines to fluoresce [6] or form fluorescent derivatives with a suitable reagent [71,77].

One method that uses the fluorescence of the amines has been described by Bowman et al [6]. The method has been successfully used to analyze biologic samples, such as blood and urine, for o-tolidine and required extraction of the compound with suitable solvents. For urine, 10 N NaOH was added to the sample, which was then extracted with benzene. A recovery of 90% was reported. The limits of detection for o-tolidine and its salts were 2 ng/ml (2 μg/liter). The major disadvantage of the method is its inability to separate o-tolidine from such related compounds as benzidine in a mixture.

Techniques in which a fluorescent derivative is formed generally use either o-phthalaldehyde or fluorescamine [71]. However, o-phthalaldehyde could not be applied to o-tolidine analyses because it failed to form a fluorescent derivative when reacted with o-tolidine [71]. Fluorescamine forms an unstable fluorescent derivative with aromatic amines [71], so it is probably unsuitable for o-tolidine fluorometry, but could be suitable for conventional colorimetry as discussed later.

In colorimetry, the biphenyl amine is reacted with a suitable reagent to form a colored complex, which is measured spectrophotometrically. A variety of colorimetric techniques have been developed, primarily for benzidine analysis of biologic specimens, and differ mainly in the reagent used. These methods have been used successfully with other related biphenyl amines and in the analysis of air samples, but only a few have actually been adapted to o-tolidine analysis. These include a qualitative method [75], a chloramine-T test [69,76], a sodium hypochlorite test [68,74], an N-(1-naphthyl)-ethylenediamine dihydrochloride test [73], and the fluorescamine reagent test [71]; they all use naphthoquinone potassium sulfonic acid as a reagent [48].

In the qualitative method [75], a bromocyanogen solution is mixed with the sample, giving rise to an orange to red color in the presence of o-tolidine. The limit of detection of this method is 50 μg of o-tolidine/liter of urine. The method is quick and simple but lacks specificity and sensitivity for monitoring o-tolidine in the air and in urine. Another disadvantage of the method is that bromocyanogen is highly toxic.

The diazotization and coupling of o-tolidine and N-(1-napthyl)-ethylenediamine dihydrochloride has been used in the analysis of o-tolidine [73]. A violet-rose complex is obtained, and the method has a reported limit of sensitivity of 2-3 μg/8 cc. The maximum concentration that can be detected without dilution is 50 μg/8 cc (6.25 μg/cc). The diazotization method may be difficult to use at very low concentrations, because the diazo compound may rapidly decompose [78].

Fluorescamine forms a stable yellow derivative with o-tolidine. It has been successfully used in the colorimetric analysis of o-tolidine and has a reported lower limit of 2 nmoles (0.3 μg) [71]. Advantages of this method over other colorimetric methods are that the reagent is colorless, thereby eliminating the need for removing the unreacted reagents, and that the colored complex is stable.

1,2-Naphthoquinone-4-potassium sulfonic acid forms a bluish-pink complex in the presence of o-tolidine and has a limit of detection of 0.05 mg/100 cc [47]. This method is not sensitive enough to monitor o-tolidine in urine samples.

Of the colorimetric methods that have been used for o-tolidine analysis, the qualitative method [75] and the 1,2-naphthoquinone-4-potassium sulfonic acid method [47] do not have the sensitivity required to adequately monitor o-tolidine in urine in the microgram range. Of the remaining four methods, the chloramine-T test [69], the sodium hypochlorite method [68], and the N-(1-naphthyl)-ethylenediamine dihydrochloride reagent method [73] are sensitive to o-tolidine in the microgram range but share the common problem of having an unstable color complex, thereby requiring quick and rapid reading.

The methods described above are nonspecific. Because o-tolidine is generally found in the same environment as benzidine and other biphenyl amines, the proper monitoring of o-tolidine in air requires a method that is both sensitive and specific for o-tolidine. Some investigators have coupled the fluorometric and colorimetric techniques discussed above with either paper [22,68,73] or thin-layer [6,71] chromatography. These chromatographic methods differ mainly in the solvents used to separate the biphenyl amines. Meigs et al [22] used reagent grade petroleum ether to separate o-tolidine from other biphenyl amines in paper chromatography but did not quantitate the o-tolidine present. Paper chromatography using an isobutanol, glacial acetic acid, and water system was coupled with the N-(1-naphthyl)-ethylenediamine dihydrochloride colorimetric method to obtain quantitative separation of o-tolidine with a level of detection of 5 μg/liter of urine [68,73]. Although these techniques can reach the desired level of sensitivity for monitoring o-tolidine in air, the procedures involved are tedious and time consuming.

Thin-layer chromatography has been used with fluorometry to obtain a qualitative separation of o-tolidine using a methanol solvent system [6] and with colorimetry using a chloroform-ethanol solvent system and 1,2-naphthoquinone-4-sulfonate reagent [71]. Quantitative separation of o-tolidine with thin-layer chromatography was accomplished using a chloroform, glacial acetic acid, and methanol solvent system to obtain separation followed by fluorescamine colorimetry [71]. The limit of sensitivity was 2 nmoles (0.3 μg). As with paper chromatography, the primary disadvantage of this method [71] is the tediousness of the operation and the time required to complete analysis.

Bowman et al [6] used a gas chromatograph equipped with a flame-ionization detector to obtain separation. The column packing was 10% OV-101 (w/w) on Gas Chrom Q (80-100 mesh) and operated with a helium flow of 100 ml/minute.

Injection port and detector temperatures were 275 C and 290 C, respectively. A temperature-programmed chromatograph (200-280 C) was used to obtain separation; o-tolidine appeared at 235 C. The sensitivity of the method was not given, but the authors did report that the method lacked the sensitivity and specificity required for trace analysis of o-tolidine.

A high-pressure liquid chromatography method has been developed and validated for benzidine in air [67]. The method has a working range of 3-130 μg/cu m and a limit of detection of 0.05 μg/sample. The method is simple and rapid compared with paper and thin-layer chromatography. Potential interferences can be overcome by changing the composition of the mobile phase or by solvent programming. This method has not been used for the analysis of o-tolidine, but because of its success in the analysis of other related biphenyl amines (those with similar physical and chemical properties) this method is judged to be acceptable for the separation and quantification of o-tolidine at the same level of detection as benzidine.

High-pressure liquid chromatography is a simple and rapid analytical procedure compared with paper and thin-layer chromatography coupled with fluorometry or colorimetry. It has a limit of detection of 0.05 μg/sample, which is four times more sensitive than the most sensitive currently available fluorometric (0.2 μg/sample) [6] or colorimetric (0.3 μg/sample) [71] method adapted for o-tolidine analysis. High-pressure liquid chromatography is therefore recommended for the analysis of o-tolidine in air.

The fluorescamine colorimetric method [71] does not have the disadvantages of the other colorimetric methods discussed above. It forms a very stable color complex with o-tolidine and is the most sensitive of these methods. This additional sensitivity would be advantageous for employee protection. The method also uses a colorless reagent, which eliminates the need for extracting the unreacted reagent. For these reasons, the fluorescamine colorimetric method of urinary analysis of o-tolidine is recommended.

The fluorometric method of Bowman et al [6] is comparable with the fluorescamine colorimetric method [71] and may be used in the analysis of urine samples. The fluorescamine colorimetric method of analysis is preferred because it is easier to perform.

## Biologic Monitoring

Aromatic diamines, such as o-tolidine and benzidine, are not normally found in the body; therefore, the detection of o-tolidine or its metabolites in the urine should be attributed to exposure to this compound. o-Tolidine may be absorbed through the lungs, the skin, or the digestive tract.

It is important to minimize or eliminate the absorption of o-tolidine by workers. This is done by adhering to stringent engineering controls and work practices. If o-tolidine or other aromatic diamines are detected by urinalysis, it may signal inadequacies in either engineering controls or work

practices; however, it should be remembered that a positive indication of diamines in the urine may result from nonoccupational sources such as medication.

Meigs et al [22,64] reported a correlation between the magnitude of exposure to biphenyl diamines, including o-tolidine, and the amount of diamines detected in the urine of workers. Following an 8-hour workshift, workers directly exposed to biphenyl diamines excreted an average of 500 μg of diamine/liter of urine. Greater quantities were excreted during the summer months than during the winter months. Foremen excreted an average of 50 μg of diamine/liter of urine following a workshift. In some instances, the authors specifically identified which diamines were in the urine. Investigation of several cases revealed the presence in the urine of some diamines to which the worker had not knowingly been exposed, thus indicating exposure of unknown origin to diamines that were either previously produced or produced in other areas of the plant. Contaminated work clothing was discovered to be the source of unexpected exposure. Improved work practices and personal hygiene were reported to have been associated with decreased urinary excretion of biphenylamine compounds. Throughout the testing period, concentrations of biphenylamines in the workplace air ranged from 2 to 87 μg/cu m, averaging 18 μg/cu m.

Further evidence of the effectiveness of improved work practices and personal hygiene in minimizing exposure of workers to diamines was reported by PF Woolrich (written communication, December 1977). Three employees worked 5 successive days wearing the same underclothing and using the same gloves. At the end of the 5th day, aromatic amine concentrations of 30, 125, and 330 mg were determined in the work clothing of the three workers. At the end of the 5th day, the corresponding concentrations of aromatic amines, measured as quinonizable substances, in the urine of the three workers were 274, 501, and 602 μg/liter, respectively, suggesting a relationship between the absorption of diamines (including o-tolidine) and skin contact with contaminated clothing.

The time span of urinary diamine excretion may be estimated from results reported by Meigs and coworkers [22]. After an accidental drenching with dichlorobenzidine, one worker had an excretion rate of urinary diamines which peaked on the day of exposure (1.13 mg/liter) and which returned to a baseline level (.043 mg/liter) the next day. This suggested to the authors that urine samples should be obtained near the end of the workshift.

Although these studies are very limited, it is concluded that the presence of biphenylamines in the urine of employees working with o-tolidine represents absorption of the compound. The measurement of urinary diamines is more of a diagnostic practice than one of compliance. Biologic monitoring provides employers with a valuable measurement technique that can be used to verify o-tolidine exposure in the individual employee.

# V. WORK PRACTICES

Health hazards from o-tolidine can be controlled by minimizing exposure through inhalation and skin contact and by a health and safety program that combines good work practices and engineering controls.

The area where o-tolidine is manufactured, processed, used, repackaged, released, handled, or stored should be designated a regulated area. This is not intended to include areas where o-tolidine tapes or kits are used for testing purposes. Skin contact with o-tolidine should be avoided. Access to the regulated area should be limited to employees having assigned duties within the area. A daily entry roster should be kept of all employees entering the regulated area and of their length of stay. This entry roster should be maintained as a part of the environmental records.

o-Tolidine should be transported or stored in sealed, intact containers. A "sealed container" is one that has been closed and kept closed to the extent that there is no release of o-tolidine. An "intact container" is one that has not deteriorated or been damaged to the extent that o-tolidine is released. It is concluded that sealed, intact containers would pose no threat of exposure to employees; therefore, it should not be necessary to comply with required monitoring and medical surveillance requirements in operations involving such containers. If, however, containers are opened or broken so that o-tolidine may be released, then all provisions of the recommended standard should apply.

Personnel working in the regulated area should be informed at least annually of the nature of the hazard of the compound, the specific nature of the operation that could result in exposure, and how to recognize and evaluate conditions and situations that may result in the release of o-tolidine. The employees should also be informed of all decontamination and emergency procedures that apply to their duties and location and especially of their role in emergency situations, such as fires or massive spills.

To prevent ingestion of o-tolidine, employees should not be allowed to eat, drink, or smoke in the regulated area, and smoking materials, food, or beverages should not be stored in this area. To counter unsuspected contamination from the container surface and process leaks, employees working where o-tolidine is stored in intact, sealed containers or contained in closed processes should wash their face, neck, hands, and forearms each time they leave the area before they engage in other activities because, even though they are wearing clothing that generally provides an effective barrier, leaks around sleeves and collars may negate some of the protective value of the clothing. Before leaving the regulated area at the end of the workday, employees should shower, shampoo, and scrub their fingernails. Users of o-tolidine test tapes and test kits need not comply with these provisions. Washing facilities should be located close to each exit. If glove boxes are used to handle o-tolidine, employees should wash their hands and arms on

completion of the assigned tasks, as a precautionary measure against possible defects in the gloves of the glove box, before engaging in activities not related to o-tolidine.

Test tapes, impregnated or coated with o-tolidine, are widely used in medical tests, such as monitoring glucose levels in the control of diabetes and for the testing of occult blood. In addition to frequent monitoring performed by patients themselves, tests are regularly performed by technicians in hospitals and clinical laboratories. The concentration of o-tolidine in test tapes is reported to be about 0.1 mg/2.5 cm (1 inch) of tape. Assuming approximately 0.5 cm of tape comes in contact with the fingers with each test, then a maximum amount of 0.02 mg might be absorbed, which is very unlikely. Some manufacturers have attached small plastic handles to the test tapes to further minimize dermal contact with o-tolidine.

Kits containing o-tolidine in solution are also used extensively by the public for testing the chlorine content in water in private swimming pools. Occupational use of similar test kits occurs in waste water treatment plants, potable water supply companies, and companies that service public and private swimming pools on a commercial basis. These test kits are usually prepared by taking 10 ml aliquots from 1- to 2-liter acidic (HCl) stock solutions containing 0.1% o-tolidine. From the test kit solution, 2-10 drops are added to 10 ml of water to be tested, the solution is capped and mixed by inverting the container, and then the developed color is compared with that on a standard color chart. Assuming there are about 20 drops/ml of water, if 5 drops of a 0.1% test solution were added to 10 ml of water, there would be approximately 0.00125 mg/drop of water being tested. In mixing water solutions improperly, an employee sometimes uses the tip of the thumb or finger, or possibly the forearm, rather than a cap to cover the opening of the container. Exposures are limited to the low o-tolidine concentration encountered during the mixing process. On rare occasions, test solutions containing 0.5% o-tolidine are used in water sanitizing procedures.

Although o-tolidine is present in test tapes and test kits, it is not believed that an occupational hazard exists from dermal contact with o-tolidine because of the low quantities available for skin absorption during the conduct of these tests.

It is essential that clothing, footwear, and headgear be clean each workday to reduce prolonged skin contact with o-tolidine. Each employee in the regulated area should therefore put on, at the beginning of each workshift, a complete set of clean work clothing (long-sleeved shirt, trousers, underwear, and footwear) before entering the regulated area. One manufacturer of o-tolidine preferred synthetic fibers to cotton because they have found that o-tolidine tends to adhere to cotton even after washing [42]. Footwear, including rubber shoes, should be cleaned inside and out at least daily and should not be taken home. Hard hats, if worn, should be over disposable or washable head covers and should be cleaned daily. In addition to this work clothing, protective clothing, including waterproof gloves and aprons or overalls, or a full-body protective suit, should be provided to employees engaged in operations in which o-tolidine is transferred from a

closed system or charged or discharged into other normally closed containers, in activities involving the opening of a closed system, or in activities involving laboratory hoods. This additional protection is believed necessary because these operations involve a greater risk of exposure to o-tolidine.

Waterproof gloves and aprons or overalls that are resistant to penetration by o-tolidine should be used while working with filters and dryers, while handling or decontaminating the exterior of filled barrels of o-tolidine, in dropping presses and filters, for taking process samples for quality checks, and for performing other routine tasks not involving maintenance. Protective clothing requirements for maintenance activities, including cleaning and decontamination of equipment and material, should be determined for each job by an industrial hygienist and the regulated-area supervisor.

Entry into confined spaces, such as tanks, pits, and process vessels that have contained o-tolidine, shall be controlled by a permit system. Permits shall be signed by an authorized employer representative certifying that prescribed precautionary measures and procedures have been followed. All lines should be disconnected or blocked off, and all valves or pumps leading to and from the vessel should be locked or tagged out while the vessel is being cleaned. The vessel should also be either washed with water and purged with air or purged with nitrogen and then with air.

The vessel should then be checked by trained personnel for fire or explosion hazard, airborne o-tolidine, possible oxygen deficiency, and concentrations of other likely contaminants to assure that no danger exists. Mechanical ventilation should be provided continuously when employees are inside the vessel. Each employee entering the vessel should be equipped with appropriate respiratory protection, a harness, and a lifeline. At least one other person, similarly equipped, should observe from outside and should maintain effective communication with the employee inside the vessel at all times.

As a supplement to engineering controls, a full-body protective suit with appropriate respiratory protection and head covering should be provided to each employee in such operations as weighing o-tolidine or charging reaction vessels for dye, pigment, and urethane manufacture [10] because of the higher risk of inhalation and skin contact. Positive pressure supplied-air respirators with full facepiece should be used whenever necessary to keep worker exposure to the lowest level possible. Full facepieces afford better fit to minimize leakage and obviate any possible problems of eye irritation. However, because contaminated clothing and equipment are primary sources of skin contact with o-tolidine, full-body protective clothing with necessary head and face protection should be used with these respirators.

Employees engaged in operations involving o-tolidine should leave their protective clothing and equipment at the exit. When workers leave the regulated area at the end of the workday, the used protective clothing and equipment should be placed in clearly labeled containers for decontamination or disposal.

Each employee involved in cleaning up leaks and spills should wear a completely enclosed full-body protective suit with either a self-contained breathing apparatus or a supplied-air respirator with auxiliary self-contained air supply. After the cleanup, the area should be decontaminated and washed, the protective clothing and equipment should be decontaminated and removed, and the employee should shower. Potassium permanganate and sodium hypochlorite have been recommended for decontamination of clothing and equipment, but data on their effectiveness as decontaminating agents were not provided (JW Meigs, written communication, December 1977). To minimize concentrations of airborne o-tolidine, employees should be prohibited from dry sweeping and dry mopping in the regulated area. The regulated area should be washed thoroughly at the end of each shift. The waste water should be collected in holding basins for decontamination with potassium permanganate or sodium hypochlorite. One o-tolidine manufacturer wipe tests work surfaces in the regulated area (PF Woolrich, written communication, December 1977). Quantitative information relating wipe test results with air levels of o-tolidine or with toxic effects of o-tolidine is not available, so its usefulness as a monitoring tool is unknown.

A clean change room, free of o-tolidine contamination and containing locker facilities, should separate regulated and nonregulated areas. The clean change room should be separated from the regulated area by a shower room. Therefore, with the exception of emergency exits, the movement of workers from clean room to regulated area should occur only through the shower area. The clean room should be under positive pressure relative to the regulated area to prevent accidental contamination of the clean area when workers move from one area to the other. Appropriate signs should be posted at the entrance informing workers of the procedures for entering and leaving the regulated area.

All workers must put on clean work clothing, including underwear, trousers, and shirt, along with footwear and the necessary protective equipment in the clean room before entering the regulated area. At no time should the regulated area be used to store protective equipment because accidental contamination by o-tolidine is possible. Before leaving the regulated area, workers should remove all protective clothing and equipment and wash their hands, forearms, face, and neck. Upon reentering the regulated area, the worker must put on the same protective clothing and equipment. To minimize traffic from regulated areas to clean areas, employers should locate toilets in rooms within regulated areas. Employees in regulated areas should wash their hands and forearms before and after using the toilet.

At the end of the workshift, protective clothing and equipment should be placed in clearly labeled containers in the regulated area for decontamination or disposal. The employees should then proceed to the shower facilities, remove all work clothing, and place it in labeled containers for laundering. Employees should shower and shampoo with soap or other detergent before entering the clean room to put on street clothing.

Laundry contaminated with o-tolidine should be transported only in sealed containers. Soap or other detergent should be used to clean work clothing.

Sodium hypochlorite has been suggested for decontamination of work clothing (PF Woolrich, written communication, December 1977). Plant personnel involved in laundering should be equipped with aprons and gloves, warned of the hazards of o-tolidine, and trained to handle contaminated clothing safely. If an outside laundry facility is used, the laundry employer must be advised of the hazards involved in handling clothing contaminated with o-tolidine and of the requirements to ensure that the laundry employees are not exposed to o-tolidine.

Employees who handle only very small quantities of o-tolidine (such as users of test tapes and water analysis kits) are considered to be at only minimal risk, and therefore the requirements for regulated areas and clean room facilities are not deemed necessary. These workers should be adequately protected from skin contact and inhalation if they perform all activities involving o-tolidine in a laboratory hood or glove box and use long-sleeved coveralls or coats and gloves of materials resistant to penetration by o-tolidine. Workers should be required to wash their hands, forearms, neck, and face with soap and water after working with o-tolidine to guard against accidental contamination.

In emergencies, the contaminated area should be evacuated immediately. Only personnel trained in emergency procedures and equipped with full-body protective clothing and proper respirators should enter the contaminated area to make repairs and decontaminate the site. All employees within the affected area at the time of emergency should be required to shower promptly. If biologic monitoring is performed, it should be conducted within 24 hours.

# VI. DEVELOPMENT OF STANDARD

## Basis for Previous Standards

No country has yet published a workplace environmental limit for o-tolidine. However, maximum allowable concentration (MAC) limits have been set by the Polish government for the chemically related substances benzidine and dianisidine (0.01 mg/cu m) [79]. Documentation supporting this value has not been found. Belgium, Great Britain, Sweden, and Japan have published work practice recommendations for o-tolidine. In Belgium, exposure to o-tolidine base (and to benzidine and its salts) is prohibited because o-tolidine is considered a carcinogen [80]. The basis for this decision was not given. Great Britain established stringent regulations, still in effect, concerning the manufacture and use of o-tolidine, which appeared with dianisidine and dichlorobenzidine on that country's 1967 controlled substances list [80,81]. These regulations are still in effect. The regulations state that all precautions must be taken to prevent workers' exposure, and they provide for extensive medical examinations every 6 months. The National Board of Occupational Safety and Health of Sweden included o-tolidine on a list of substances that could be manufactured or used only if special instructions by the labor inspectorate were followed [80,82,83]. Similarly, in Japan, special permission must be obtained from the labor department to use or manufacture o-tolidine. When this permission is granted, strict procedures that prevent worker exposure and provide for regular medical examinations must be followed [80]. The Soviet Union reportedly no longer produces o-tolidine [84].

## Basis for the Recommended Standard

### (a) Permissible Exposure Limits

A few studies have been found that give results of human exposure to o-tolidine, usually in conjunction with exposure to other related diamines, eg, benzidine, dichlorobenzidine, and dianisidine [16,19,21-23,85]. A number of animal studies have been found in which the effects of exposure to o-tolidine by itself were investigated [17,26,28-30,33,35,38,44,49]. Most occupational exposures involve a mixture of biphenyl amine compounds, including benzidine, o-tolidine, dichlorobenzidine, and dianisidine [19,21-23].

There is a report stating that inhalation of o-tolidine hydrochloride causes nasal irritation in humans [16]. o-Tolidine is absorbed through the skin of humans without apparent skin irritation [17] and is subsequently eliminated in the urine [17,22].

Although cancer has not been observed in humans exposed to o-tolidine alone, workers exposed to a combination of benzidine and o-tolidine have developed bladder cancer [20,21]. Benzidine is a known human bladder carcinogen [15], but these reports [20,21] do not give sufficient data to determine if the cancers were induced by benzidine alone, o-tolidine alone, or both compounds.

o-Tolidine (or its metabolites) is carcinogenic in some animals [29,33-35]. The majority of rats developing cancers had carcinomas of the Zymbal glands, mammary gland adenocarcinomas, and hepatocarcinomas [33-35]. Tumors of lesser frequency included skin cancers, stomach papillomas, small intestine adenocarcinomas, one uterine leiomyosarcoma, preputial sebaceous gland tumors, and reticulosarcomas. One of four dogs fed o-tolidine for 8-9 months developed bladder cancer after 8 years [29].

Ames assays showed o-tolidine to be mutagenic in two studies [41,43]. However, another, more comprehensive, study [42] reported negative findings for o-tolidine. o-Tolidine was shown to depress thymidine incorporation into testicular DNA [40], indicating a diminution of DNA synthesis directly related to o-tolidine exposure. o-Tolidine had mutagenic effects on rat embryo cells in cell culture; when the transformed cells were transplanted into rats, they developed into tumors [39].

o-Tolidine did not cause deformed rat embryos in dams receiving a total dose of 30 mg in three successive daily sc injections [45], but 8% of the fetuses were resorbed. Organ cultures of embryonic kidneys from pregnant mice given sc injections of 2 mg/day for 19-20 days exhibited epithelial hyperplasia and "other cellular changes" that were not seen in the controls [44]; this suggests that o-tolidine may have transplacental effects on embryogenesis.

There are important similarities between o-tolidine and benzidine, a known human bladder carcinogen. Structurally, o-tolidine is the 3,3'-dimethyl substituted form of benzidine, and its physical and chemical properties closely parallel those of benzidine [5,6]. Both are absorbed through human skin and are excreted in the urine either unchanged or as structurally analogous conjugates [22,47,58]. The metabolic pathways of both are similar; both undergo acetylation, hydroxylation, or sulfate esterification [22,47,50,56,58]. Neither compound has induced bladder cancer in rats [15,62], but each has caused cancer in other tissues and organs [15,62]. Bladder cancer in dogs has been observed with each compound [29,86], although the evidence for o-tolidine consists of only one dog with cancer of four dogs exposed, 8 years after an 8- to 9-month feeding period [29].

Because tests with o-tolidine, like benzidine, have resulted in mutagenic effects in test systems and because cancer has occurred in rodents as a result of o-tolidine absorption, there is substantial reason to believe that o-tolidine will induce bladder cancer in humans. Therefore, it is recommended that o-tolidine be handled as a suspect human carcinogen. Because of this conclusion and since it is not possible at this time to establish an exposure level at which o-tolidine is known to be harmless, it is recommended that exposure to o-tolidine be kept as low as possible through strict adherence to a program of monitoring, engineering controls, and stringent work practices. The recommended sampling and analytical method for measuring o-tolidine in air is one that has been experimentally confirmed for benzidine and, because of the physical and chemical similarities of the two compounds, the method is judged to be suitable for o-tolidine. The lowest amount of o-tolidine reliably measured quantitatively by this method is estimated to be 0.2

μg/sample. If an air sample is collected at 0.2 liters/minute for 60 minutes, this quantity of o-tolidine is equivalent to 20μg/cu m, so this concentration represents the lowest level at which a reliable quantitative estimate of exposure to o-tolidine can be determined. Therefore, it is recommended that occupational exposure be controlled so that no worker will be exposed at a concentration of o-tolidine in excess of 20μg/cu m in air determined from an air sample collected at 0.2 liters/minute for 60 minutes.

It is of interest that the International Agency for Research on Cancer (IARC) has also listed o-tolidine as a cancer suspect agent in humans [87,88].

Although o-tolidine is present in test tapes and test kits used for the determination of glucose in blood or urine, blood in urine or feces, or chlorine in water, it is not believed that an occupational hazard exists either from airborne o-tolidine or from dermal contact that may result from such use. It is concluded that users of test tapes and test kits containing o-tolidine should be excluded from the monitoring and surveillance requirements of this recommended standard. However, all provisions of the standard should apply where o-tolidine is used in the manufacturing and formulating of test tapes, test kits, and test solutions.

The presence of o-tolidine or its metabolites in the urine provides a means for the biologic monitoring of o-tolidine exposure, even though such monitoring has not been sufficiently investigated to warrant requiring it as part of medical monitoring. However, it may still be a useful adjunct to monitoring of the workplace air to gain information on unknown sources of exposure, to identify unanticipated excursions, and to recognize poor work practices.

(b) Sampling and Analysis

A filter is suitable for capturing the o-tolidine aerosol. The filter should be made of glass fibers to minimize pressure drop. The filter should be backed by a silica gel tube because o-tolidine has a low but distinct vapor pressure. High-pressure liquid chromatography has been shown to be a good method for benzidine and should be similarly useful for the analysis of o-tolidine.

(c) Medical Surveillance

Comprehensive preplacement and annual examinations should be made available to all workers occupationally exposed to o-tolidine. Workers should be informed that o-tolidine administration has resulted in nasal irritation in humans and that o-tolidine has caused kidney damage [16] or cancer of the skin, glands, or internal organs [29,33] in animals.

Because of the possibility of kidney damage [16,26], workers occupationally exposed to o-tolidine should have quarterly urine examinations, including a complete urinalysis and microscopic examination of the urine for evidence of abnormal cells indicative of kidney damage or neoplasms. The

test should be repeated within 1 week to confirm any abnormal results found. If the abnormalities are confirmed, the worker should be referred to a physician for a comprehensive urologic evaluation.

(d) Personal Protective Equipment and Clothing

Employees working with o-tolidine change clothes at the beginning and end of work shifts. Work clothes may become contaminated with dust, so they must be kept in a separate locker, away from street clothes. Clean work clothes should be worn each shift. If work clothes are not changed after each shift and laundered, absorption of o-tolidine through the skin may be facilitated by both the increased time in which skin contact is maintained and by the buildup of o-tolidine in the clothing [22]. Measurement of o-tolidine in the urine of workers confirmed this in one operation [22]. Soiled work clothes should be stored in covered containers until they are laundered either at the plant or, if an outside laundry facility is used, the launderers should be advised of the hazards and proper procedures involved in handling contaminated work clothing. Sodium hypochlorite has been used for decontamination prior to laundering, but no data supporting its effectiveness have been found. The employer in charge of laundering should emphasize precautionary measures to avoid exposure to o-tolidine from handling contaminated work clothes. Gloves and aprons resistant to o-tolidine should be worn, and skin contact with o-tolidine should be avoided. When exposure to dust or mist containing o-tolidine occurs during emergencies, maintenance operations, or special processes, use of the respirators specified in Chapter I, Section 3 (b) and full-body skin protection should be observed.

(e) Informing Employees of Hazards

Continuing education is an important part of a preventive hygiene program for employees exposed to o-tolidine. Workers should be instructed periodically by properly trained persons about possible sources of exposure to o-tolidine, engineering and work practice controls in use or being planned to limit exposure, and on monitoring procedures used to check control procedures. It should also be explained that o-tolidine may be readily absorbed through the intact skin as well as by inhalation or ingestion and that exposure to it poses a risk of damage to the urinary tract, primarily cancer of the urinary bladder. The function of environmental monitoring equipment, such as personal samplers, should be explained, so that employees understand their part in environmental monitoring. Medical monitoring procedures and their importance in detecting possible adverse health effects should be explained.

(f) Work Practices

Because o-tolidine can be readily absorbed through intact skin and mucous membranes, special work practices are essential. It is especially important that the use of regulated areas and clean rooms and the procedures for sanitation, maintenance, and emergencies in the control of airborne o-tolidine be understood and followed by workers occupationally exposed to the chemical.

If o-tolidine is handled or stored in intact, sealed containers, the requirements of regulated areas should not be necessary. However, if containers are opened, the requirement for a regulated area applies.

(g) Monitoring and Recordkeeping Requirements

Industrial hygiene surveys should be conducted after the promulgation of a standard based on these recommendations and within 14 days of any process change.

If the concentration of airborne o-tolidine in a regulated area exceeds the recommended occupational exposure limit, proper engineering and work practice control measures should be initiated. Sampling should be repeated until two consecutive determinations at least 1 week apart show that airborne concentrations of o-tolidine are below the recommended occupational exposure limit. If this survey reveals that the airborne concentration is below the recommended occupational exposure limit, then the survey need only be repeated annually.

Medical records for all employees occupationally exposed to o-tolidine should be kept for 30 years after the termination of employment. Records of environmental exposures to o-tolidine should be included with the worker's medical records. These records should be available to the designated medical representatives of the employer, employee, Secretary of Health, Education, and Welfare, and of the Secretary of Labor.

# VII. RESEARCH NEEDS

Although o-tolidine is not a new compound and has been used for a century as an indicator in analytical chemistry and as an intermediate in the synthesis of approximately 100 dyes [4], relatively little has been published about its effects on biologic systems. In particular, there is a scarcity of information on how o-tolidine affects humans.

Before better dose-response relationships can be delineated, more experiments with animals are needed. As presented in Chapter III, the currently available experimental data on rats exposed to o-tolidine indicate that, as with benzidine, it can cause cancer in a number of organ systems in the rat, but it does not cause bladder cancer. This is also apparently true for the hamster. Attempts should be made to find an animal model in which bladder cancer could be identified from administration of o-tolidine, benzidine, or other diphenyl amines. This would be helpful in evaluating bladder cancer in humans associated with these amines. Epidemiologic studies on workers exposed to o-tolidine are especially needed to investigate the problem of o-tolidine-related bladder tumors in humans. Cell- and organ-culture studies, including host-mediated assays, would be useful to evaluate the significance of genetic alterations from o-tolidine. The renal effects from o-tolidine, both alone and associated with exposure to other chemicals, especially other aromatic amines, should be addressed.

The metabolism of o-tolidine resembles that of benzidine, a known human bladder carcinogen. Additional studies are needed to further elucidate o-tolidine metabolism, to compare it to that of benzidine, and to identify those metabolites that may be toxic or carcinogenic. The possibility exists that dyes made from o-tolidine might release free o-tolidine in the body. This should be investigated.

Workers who use o-tolidine coated or impregnated test tapes or water analysis test kits containing o-tolidine are judged at this time to be at negligible risk from the chemical. (This is based on professional estimates and calculations because investigative data are lacking.) Studies should be conducted to ascertain whether such users absorb o-tolidine from skin contact in quantities sufficient to pose a risk to worker health.

Validation of the sampling and analytical methods recommended for o-tolidine is needed, even though they have been tested for benzidine and are judged to be effective for o-tolidine.

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