OCCUPATIONAL SAFETY AND HEALTH GUIDELINE
FOR ANISIDINE (o-, p-ISOMERS)

INTRODUCTION
This guideline summarizes pertinent information about anisidine (both the ortho- and the para-isomers) for workers and employers as well as for physicians, industrial hygienists, and other occupational safety and health professionals who may need such information to conduct effective occupational safety and health programs. Recommendations may be superseded by new developments; readers are therefore advised to regard these recommendations as general guidelines and to determine periodically whether new information is available.

SUBSTANCE IDENTIFICATION

o-ANISIDINE
- Formula
  \[ \text{NH}_2\text{C}_6\text{H}_4\text{OCH}_3 \]
- Structure

- Synonyms
  o-Methoxyaniline, 2-methoxyaniline, 2-aminoanisole, o-anisylamine, 2-methoxybenzenamine, o-methoxyphenylamine
- Identifiers
  1. CAS No.: 90-04-0
  2. RTECS No.: BZ5410000
  3. DOT UN: 2431 55
  4. DOT label: St. Andrew's Cross
- Appearance and odor
  The ortho- form of anisidine is a reddish or yellowish liquid that has a characteristic amine (fishy) odor.

p-ANISIDINE
- Formula
  \[ \text{NH}_2\text{C}_6\text{H}_4\text{OCH}_3 \]
- Structure

- Synonyms
  p-Methoxyaniline, 4-methoxyaniline, 4-methoxybenzenamine, p-anisylamine, p-aminoanisole, 4-aminoanisole
- Identifiers
  1. CAS No.: 104-94-9
  2. RTECS No.: BZ5450000
  3. DOT UN: None
  4. DOT label: None
- Appearance and odor
  The para- form of anisidine is a light reddish-brown, fused crystalline mass that has a characteristic amine (fishy) odor.

CHEMICAL AND PHYSICAL PROPERTIES

o-ANISIDINE
- Physical data
  1. Molecular weight: 123.2
  2. Boiling point (at 760 mm Hg): 225°C (437°F)
  3. Specific gravity (water = 1): 1.1 at 20°C (68°F)
  4. Vapor density (air = 1 at boiling point of o-anisidine): 4.3
  5. Melting point: 5°C (41°F)
  6. Vapor pressure at 20°C (68°F): Less than 0.1 mm Hg
7. Solubility: Practically insoluble in water; miscible with alcohol and ether

8. Evaporation rate: Data not available

• Reactivity

1. Conditions contributing to instability: o-Anisidine is volatile with steam and unstable with heat.

2. Incompatibilities: Fires and explosions may result from contact with strong oxidizers.

3. Hazardous decomposition products: Toxic gases (such as oxides of nitrogen and carbon monoxide) may be released during the thermal decomposition of anisidine.

4. Special precautions: Liquid anisidine attacks some coatings and some forms of plastic and rubber.

• Flammability

The National Fire Protection Association has assigned a flammability rating of 1 (slight fire hazard) to o-anisidine.

1. Flash point: 118°C (244°F) (open cup)

2. Autoignition temperature: Data not available

3. Flammable limits in air: Data not available

4. Extinguisher: Use dry chemical, carbon dioxide, Halon®, water spray, or standard foam to fight small fires involving anisidine; use water spray, fog, or standard foam to fight large fires involving anisidine.

Fires involving anisidine should be fought upwind and from the maximum distance possible. Isolate the hazard area and deny access to unnecessary personnel. Emergency personnel should stay out of low areas and ventilate closed spaces before entering. Containers of anisidine may explode in the heat of the fire and should be moved from the fire area if it is possible to do so safely. If this is not possible, cool containers from the sides with water until well after the fire is out. Stay away from the ends of containers. Personnel should withdraw immediately if they hear a rising sound from a venting safety device or if a container becomes discolored as a result of fire. Dikes should be used to contain fire-control water for later disposal. If a tank car or truck is involved in a fire, personnel should isolate an area of a half mile in all directions. Firefighters should wear a full set of protective clothing (including a self-contained breathing apparatus) when fighting fires involving anisidine. Chemical protective clothing that is specifically recommended for anisidine may not provide thermal protection unless stated by the clothing manufacturer. Firefighters’ protective clothing may not provide protection against permeation by anisidine.

**p-ANISIDINE**

• Physical data

1. Molecular weight: 123.2

2. Boiling point (at 760 mm Hg): 246°C (475.4°F)

3. Specific gravity (water = 1): 1.07 at 57°C (134.6°F)

4. Vapor density (air = 1 at boiling point of p-anisidine): 4.3

5. Melting point: 57°C (134.6°F)

6. Vapor pressure at 20°C (68°F): Less than 0.1 mm Hg

7. Solubility: Slightly soluble in water; freely soluble in methanol, ethanol, and ether

8. Evaporation rate: Data not available

• Reactivity

1. Conditions contributing to instability: p-Anisidine is unstable with heat.

2. Incompatibilities: Fires and explosions may result from contact with strong oxidizers.

3. Hazardous decomposition products (both isomers): Toxic gases (such as oxides of nitrogen and carbon monoxide) may be released during the thermal decomposition of anisidine.

4. Special precautions: Liquid anisidine attacks some coatings and some forms of plastic and rubber.

• Flammability

p-Anisidine is considered a severe fire hazard, but the National Fire Protection Association has not assigned a flammability hazard rating to this chemical.

1. Flash point: 30°C (86°F) (closed cup)

2. Autoignition temperature: Data not available

3. Flammable limits in air: Data not available

4. Extinguisher: Use dry chemical, carbon dioxide, Halon®, water spray, or standard foam to fight small fires involving anisidine; use water spray, fog, or standard foam to fight large fires involving anisidine.

Fires involving anisidine should be fought upwind and from the maximum distance possible. Isolate the hazard area and deny access to unnecessary personnel. Emergency personnel should stay out of low areas and ventilate closed spaces before entering. Containers of anisidine may explode in the heat of the fire and should be moved from the fire area if it is possible to do so safely. If this is not possible, cool containers from the sides with water until well after the fire is out. Stay away from the ends of containers. Personnel should withdraw immediately if they hear a rising sound from a venting safety device or if a container becomes discolored as a result of fire. Dikes should be used to contain
fire-control water for later disposal. If a tank car or truck is involved in a fire, personnel should isolate an area of a half mile in all directions. Firefighters should wear a full set of protective clothing (including a self-contained breathing apparatus) when fighting fires involving anisidine. Chemical protective clothing that is specifically recommended for anisidine may not provide thermal protection unless stated by the clothing manufacturer. Firefighters’ protective clothing may not provide protection against permeation by anisidine.

EXPOSURE LIMITS

• OSHA PEL
The current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for anisidine (both isomers) is 0.5 mg/m³ (0.1 ppm) as an 8-hr time-weighted average (TWA). The OSHA PEL also bears a “Skin” notation, which indicates that the cutaneous route of exposure (including mucous membranes and eyes) contributes to overall exposure [29 CFR 1910.1000, Table Z-1-A].

• NIOSH REL
The National Institute for Occupational Safety and Health (NIOSH) has established a recommended exposure limit (REL) of 0.5 mg/m³ as an 8-hr TWA for both the para- and ortho-isomers. The NIOSH REL also bears a “Skin” notation. NIOSH considers the ortho-isomer to be a potential occupational carcinogen; exposure should therefore be limited to the lowest feasible concentration [NIOSH 1992].

• ACGIH TLV®
The American Conference of Governmental Industrial Hygienists (ACGIH) has assigned both isomers of anisidine a threshold limit value (TLV) of 0.5 mg/m³ (0.1 ppm) as a TWA for a normal 8-hr workday and a 40-hr workweek. The ACGIH has also assigned a “Skin” notation to anisidine [ACGIH 1991b].

Rationale for limits
The limits are based on the risk of systemic effects associated with exposure to anisidine. NIOSH considers o-anisidine to be a potential occupational carcinogen because of positive carcinogenic results in studies of rats and mice.

HEALTH HAZARD INFORMATION

• Routes of exposure
Exposure to o- and p-anisidine can occur through inhalation of the dust or vapor, ingestion, or eye or skin contact. Anisidine is readily absorbed through the skin.

• Summary of toxicity
1. Effects on Animals: Anisidine causes methemoglobinemia and is a carcinogen in experimental animals. The toxicologic literature is often unclear about the particular isomer or mixture of isomers involved in a given study; when information about the specific form of anisidine is available, it is included in the following discussion. The oral LD₅₀ in rats is 2,000 mg/kg for o-anisidine and 810 mg/kg for p-anisidine [NIOSH 1991]. Mice exposed to anisidine (isomer not specified) at 2 to 6 ppm for 2 hr/day for 1 year developed anemia and reticulocytosis [Proctor et al. 1988]. Animals that received subacute doses of either of the anisidine isomers developed anemia and other blood changes and showed signs of kidney damage at autopsy [IARC 1982]. Mice and rats fed diets containing up to 30,000 mg/kg o-anisidine hydrochloride for 7 weeks showed reductions in weight gain, and animals fed lower doses for the same period showed blackened, granular, and/or enlarged spleens [IARC 1982]. Eight-week feeding studies involving p-anisidine hydrochloride caused similar effects in rats and mice [IARC 1982]. o-Anisidine hydrochloride in the diet caused transitional-cell carcinomas of the urinary bladder in both rats and mice [IARC 1982]. The rats in this study also had statistically increased numbers of renal transitional-cell carcinomas and thyroid follicular-cell carcinomas [IARC 1982]. p-Anisidine hydrochloride did not cause cancer in mice, and the results of a carcinogenicity bioassay in rats were inconclusive [IARC 1982]. On the basis of this evidence, the International Agency for Research on Cancer (IARC) has concluded that sufficient evidence exists for the carcinogenicity of o-anisidine hydrochloride in animals but not for p-anisidine [IARC 1982].

2. Effects on Humans: Anisidine causes methemoglobinemia in humans. Some members of a group of workers exposed to 0.4 ppm of anisidine (isomer not specified) for 6 months (3.5 hr/day) did not exhibit clinical signs of anemia but showed the following blood changes: increased methemoglobin, sulfhemoglobin, and HbF body formation [Proctor et al. 1988]. Anisidine (form not specified) causes dermatitis on repeated or prolonged contact and is also known to be a mild skin sensitizer [Proctor et al. 1988].

• Signs and symptoms of exposure
1. Acute exposure: Acute exposure to anisidine can cause methemoglobinemia, including bluish coloring of the skin, ear lobes, and lips; headache; dizziness; drowsiness; nausea and vomiting; and, in severe cases, unconsciousness and death.

2. Chronic exposure: Chronic exposure to anisidine can cause anemia, pallor, methemoglobinemia, fatigue, shortness of breath, and palpitations. Dermatitis and skin sensitization (which include redness and itching of the skin, blisters, swelling, and pain) may also occur. Because three cancer sites (bladder, kidney, and thyroid) have been found in animals, exposure to o-anisidine may cause cancers in humans.
• Emergency procedures

Keep unconscious victims warm and on their sides to avoid choking if vomiting occurs. Initiate the following emergency procedures:

1. Eye exposure: Tissue irritation may result from exposure to particulates or concentrated solutions, vapors, mists, or aerosols of anisidine. Immediately and thoroughly flush the eyes with large amounts of water, occasionally lifting the upper and lower eyelids.

2. Skin exposure: Skin irritation may result. Immediately remove contaminated clothing and thoroughly wash contaminated skin with soap and water.

3. Inhalation exposure: If the particulates, vapors, mists, or aerosols of anisidine are inhaled, move the victim to fresh air immediately. Have the victim blow his or her nose, or use a soft tissue to swab particulates from the nostrils.

If the victim is not breathing, clean any chemical contamination from the victim’s lips and perform cardiopulmonary resuscitation (CPR); if breathing is difficult, give oxygen.

4. Ingestion exposure: Take the following steps if anisidine or a solution containing it is ingested:

—Have the victim rinse the contaminated mouth cavity several times with a fluid such as water.
—Have the victim drink a glass (8 oz) of fluid such as water.
—Induce vomiting by giving syrup of ipecac as directed on the package. If ipecac is unavailable, have the victim touch the back of the throat with a finger until productive vomiting ceases.
—Do not force an unconscious or convulsing person to drink fluid or to vomit.

5. Rescue: Remove an incapacitated worker from further exposure and implement appropriate emergency procedures (e.g., those listed on the material safety data sheet required by OSHA’s hazard communication standard [29 CFR 1910.1200]). All workers should be familiar with emergency procedures and the location and proper use of emergency equipment.

EXPOSURE SOURCES AND CONTROL METHODS

The following operations may involve anisidine and may result in worker exposures to this substance:

—Manufacture of azo- or triphenyl-methane dyes and intermediates
—Production of a derivative that is used as an expectorant in drugs for humans and animals and as a muscle relaxant in drugs for humans
—Preparation of organic compounds, synthesis of guaiacol and hair dyes
—Use of anisidine as a corrosion inhibitor for steel storage, as an antioxidant for some polymeric resins, and as a dye assist
—Use of anisidine as an analytic agent and as an intermediate in the synthesis of compounds in the form of liquid crystals
—Use of anisidine in the production of pharmaceutical and textile-processing chemicals

The following methods are effective in controlling worker exposures to anisidine, depending on the feasibility of implementation:

—Process enclosure
—Local exhaust ventilation
—General dilution ventilation
—Personal protective equipment

Good sources of information about control methods are as follows:


MEDICAL MONITORING

Workers who may be exposed to chemical hazards should be monitored in a systematic program of medical surveillance that is intended to prevent occupational injury and disease. The program should include education of employers and workers about work-related hazards, placement of workers in jobs that do not jeopardize their safety or health, early detection of adverse health effects, and referral of workers for diagnosis and treatment. The occurrence of disease or other work-related adverse health effects should prompt
immediate evaluation of primary preventive measures (e.g., industrial hygiene monitoring, engineering controls, and personal protective equipment). A medical monitoring program is intended to supplement, not replace, such measures. To place workers effectively and to detect and control work-related health effects, medical evaluations should be performed (1) before job placement, (2) periodically during the term of employment, and (3) at the time of job transfer or termination.

- **Preplacement medical evaluation**

Before a worker is placed in a job with a potential for exposure to anisidine, a licensed health care professional should evaluate and document the worker’s baseline health status with thorough medical, environmental, and occupational histories, a physical examination, and physiologic and laboratory tests appropriate for the anticipated occupational risks. These should concentrate on the function and integrity of the blood, liver, kidneys, and cardiovascular system. A complete blood count, reticulocyte count, and urinalysis should be done.

A preplacement medical evaluation is recommended to assess an individual’s suitability for employment at a specific job and to detect and assess medical conditions that may be aggravated or may result in increased risk when a worker is exposed to anisidine at or below the prescribed exposure limit. The licensed health care professional should consider the probable frequency, intensity, and duration of exposure as well as the nature and degree of any applicable medical condition. Such conditions (which should not be regarded as absolute contraindications to job placement) include a history and other findings consistent with chronic blood disorders, chronic liver or kidney disease, or chronic cardiovascular disease.

- **Periodic medical examinations and biological monitoring**

Occupational health interviews and physical examinations should be performed at regular intervals during the employment period, as mandated by any applicable Federal, State, or local standard. Where no standard exists and the hazard is minimal, evaluations should be conducted every 3 to 5 years or as frequently as recommended by an experienced occupational health physician. Additional examinations may be necessary if a worker develops symptoms attributable to anisidine exposure. The interviews, examinations, and medical screening tests should focus on identifying the adverse effects of anisidine on the blood, liver, kidneys, and cardiovascular system. A complete blood count, reticulocyte count, and urinalysis should be performed. Current health status should be compared with the baseline health status of the individual worker or with expected values for a suitable reference population.

Biological monitoring involves sampling and analyzing body tissues or fluids to provide an index of exposure to a toxic substance or metabolite. The measurement of methemoglobin in the blood is a nonspecific, qualitative indicator of exposure to a variety of chemical agents such as anisidine that induce the formation of methemoglobin. Methemoglobin levels cannot be linked quantitatively to airborne concentrations of anisidine; methemoglobin monitoring thus serves only as a screening test to identify workers who may be overexposed. A methemoglobin level of 1.5% of total hemoglobin is recommended by some sources as a biological exposure index. Blood specimens should be collected while exposure to anisidine is occurring, and, if possible, the specimens should be analyzed at the place of collection.

- **Medical examinations recommended at the time of job transfer or termination**

The medical, environmental, and occupational history interviews, the physical examination, and selected physiologic or laboratory tests that were conducted at the time of job placement should be repeated at the time of job transfer or termination. Any changes in the worker’s health status should be compared with those expected for a suitable reference population.

**WORKPLACE MONITORING AND MEASUREMENT**

A worker’s exposure to airborne anisidine (α-, β-isomers) is determined by using XAD-2 solid sorbent tubes (150/75-mg sections, 20/50 mesh). Samples are collected at a maximum flow rate of 1 liter/min until a maximum air volume of 320 liters is collected. The sample is then treated with methanol to extract the anisidine. Analysis is conducted by high-pressure liquid chromatography using an ultraviolet absorption detector. The limit of detection for this procedure is 0.35 μg per sample. This method is described in Method 2514 of the *NIOSH Manual of Analytical Methods* [NIOSH 1984].

**PERSONAL HYGIENE**

Workers should immediately and thoroughly wash with soap and water any areas of the skin that have come in contact with the substance because anisidine can be absorbed through the skin in toxic amounts.

Clothing and shoes contaminated with anisidine should be removed immediately, and provisions should be made for safely removing this chemical from these articles. Persons laundering contaminated clothing should be informed about the hazardous properties of anisidine, particularly its potential for being absorbed through the skin in toxic amounts.
A worker who handles anisidine should thoroughly wash hands, forearms, and face with soap and water before eating, using tobacco products, or using toilet facilities.

Workers should not eat, drink, or use tobacco products in areas where anisidine or a solution containing anisidine is handled, processed, or stored.

**STORAGE**

Anisidine should be stored in a cool, dry, well-ventilated area in tightly sealed containers that are labeled in accordance with OSHA's hazard communication standard [29 CFR 1910.1200]. Storage areas for p-anisidine should be suitable for combustible solids. Containers of anisidine should be protected from physical damage and should be separated from oxidizing agents, heat, sparks, and open flame. Metal conveying and storage equipment should be grounded and bonded to prevent sparks. Bulk storage systems should be of explosionproof design. Because containers that formerly contained anisidine may still hold product residues, they should be handled appropriately.

**SPILLS AND LEAKS**

In the event of a spill or leak involving anisidine, persons not wearing protective equipment and clothing should be restricted from contaminated areas until cleanup is complete. The following steps should be undertaken following a spill or leak:

1. Do not touch the spilled material; stop the leak if it is possible to do so without risk.
2. Notify safety personnel.
3. Remove all sources of heat and ignition.
4. Ventilate potentially explosive atmospheres.
5. Make sure that cleanup personnel wear appropriate protective clothing and equipment to prevent skin and eye contact and inhalation.
6. For small dry spills, use a clean shovel and place the material in a clean, dry container; cover and remove the container from the spill area.
7. Absorb small liquid spills with sand or other noncombustible absorbent material and place the material in a covered container for later disposal.
8. For large liquid spills, build dikes far ahead of the spill to contain the anisidine for later reclamation or disposal.

**SPECIAL REQUIREMENTS**

U.S. Environmental Protection Agency (EPA) requirements for emergency planning, reportable quantities of hazardous release, community right-to-know, and hazardous waste management may change over time. Users are therefore advised to determine periodically whether new information is available.

- **Emergency planning requirements**
  Anisidine is not subject to EPA emergency planning requirements under the Superfund Amendments and Reauthorization Act (SARA) [42 USC 11022].

- **Reportable quantity requirements for hazardous releases**
  Employers are not required by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [40 CFR 355.40] to notify the National Response Center of an accidental release of anisidine; there is no reportable quantity for anisidine.

- **Community right-to-know requirements**
  Employers are not required by SARA to submit a Toxic Chemical Release Inventory Form (Form R) to EPA reporting the amount of anisidine emitted or released from their facility.

- **Hazardous waste management requirements**
  EPA considers a waste to be hazardous if it exhibits any of the following characteristics: ignitability, corrosivity, reactivity, or toxicity as defined in 40 CFR 261.21-261.24. Although anisidine is not specifically listed as a hazardous waste under the Resource Conservation and Recovery Act (RCRA) [42 USC 6901 et seq.], EPA requires employers to treat waste as hazardous if it exhibits any of the characteristics discussed above.

Providing detailed information about the removal and disposal of specific chemicals is beyond the scope of this guideline. The U.S. Department of Transportation, EPA, and State and local regulations should be followed to ensure that removal, transport, and disposal of anisidine are conducted in accordance with existing regulations. To be certain that chemical waste disposal meets EPA regulatory requirements, employers should address any questions to the RCRA hotline at (800) 424-9346 or at (202) 382-3000 in Washington, D.C. In addition, relevant State and local authorities should be contacted for information about their requirements for waste removal and disposal.

**RESPIRATORY PROTECTION**

- **Conditions for respirator use**
  Good industrial hygiene practice requires that engineering controls be used where feasible to reduce workplace concentrations of hazardous materials to the prescribed exposure limit. However, some situations may require the use of respirators to control exposure. Respirators must be worn if
the ambient concentration of anisidine exceeds prescribed exposure limits. Respirators may be used (1) before engineering controls have been installed, (2) during work operations such as maintenance or repair activities that involve unknown exposures, (3) during operations that require entry into tanks or closed vessels, and (4) during emergencies. Workers should use only respirators that have been approved by NIOSH and the Mine Safety and Health Administration (MSHA).

- **Respiratory protection program**

Employers should institute a complete respiratory protection program that, at a minimum, complies with the requirements of OSHA's respiratory protection standard [29 CFR 1910.134]. Such a program must include respirator selection, an evaluation of the worker's ability to perform the work while wearing a respirator, the regular training of personnel, fit testing, periodic workplace monitoring, and regular respirator maintenance, inspection, and cleaning. The implementation of an adequate respiratory protection program (including selection of the correct respirator) requires that a knowledgeable person be in charge of the program and that the program be evaluated regularly. For additional information on the selection and use of respirators and on the medical screening of respirator users, consult the NIOSH Respirator Decision Logic [1987b] and the NIOSH Guide to Industrial Respiratory Protection [1987a].

**PERSONAL PROTECTIVE EQUIPMENT**

Gloves and protective clothing should be worn to prevent any skin contact with anisidine. Chemical protective clothing should be selected on the basis of available performance data, manufacturers' recommendations, and evaluation of the clothing under actual conditions of use. No reports have been published on the resistance of various protective clothing materials to anisidine permeation. If permeability data are not readily available, protective clothing manufacturers should be requested to provide information on the best chemical protective clothing for workers to wear when they are exposed to anisidine.

If anisidine is dissolved in water or an organic solvent, the permeation properties of both the solvent and the mixture must be considered when selecting personal protective equipment and clothing.

Safety glasses, goggles, or face shields should be worn during operations in which anisidine dust or liquid might contact the eyes. Eyewash fountains and emergency showers should be available within the immediate work area whenever the potential exists for eye or skin contact with anisidine. Contact lenses should not be worn if the potential exists for anisidine exposure.

**REFERENCES CITED**


