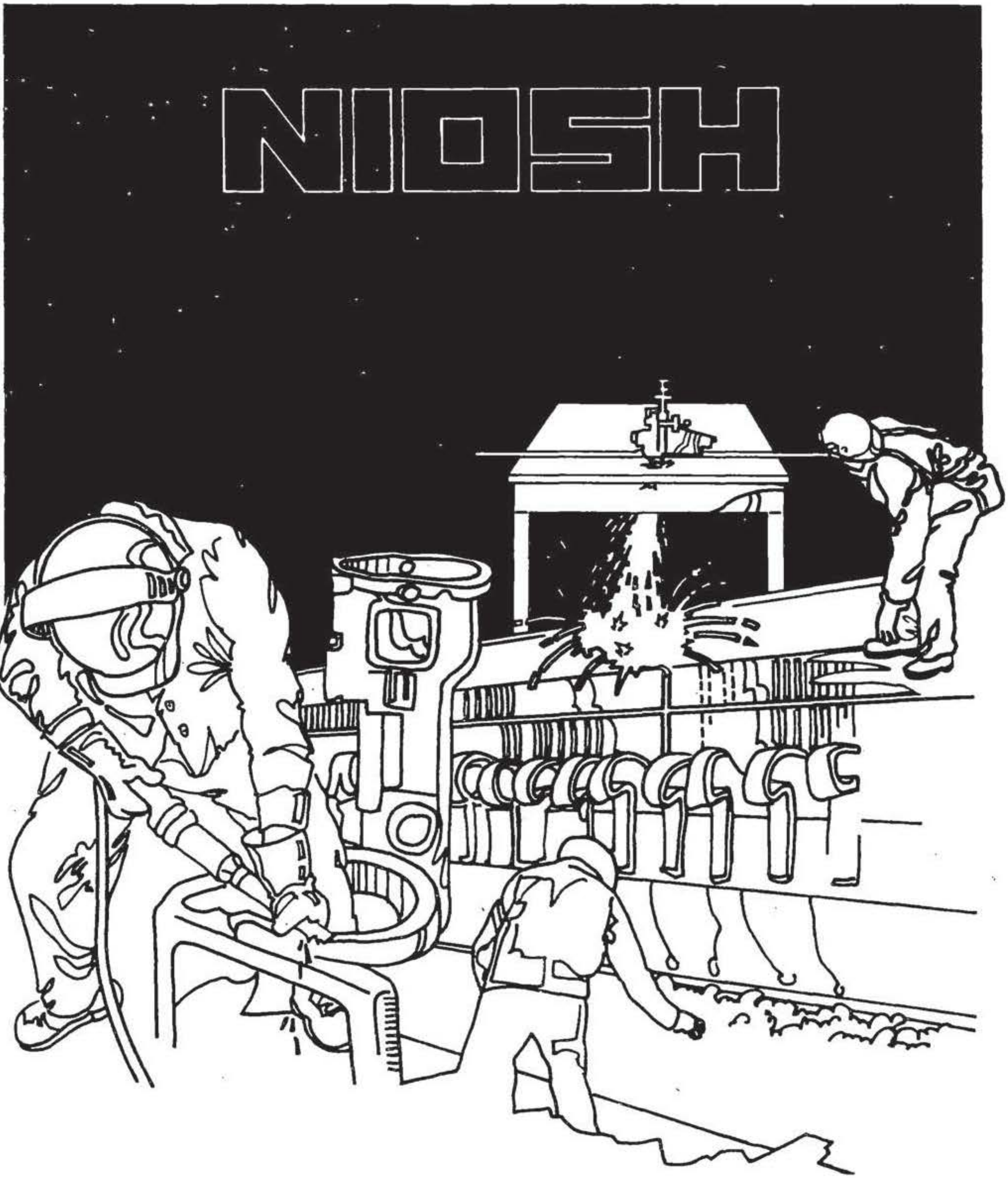
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ■ Public Health Service
Centers for Disease Control ■ National Institute for Occupational Safety and Health



Health Hazard Evaluation Report

HETA 82-326-1420
KEYSTONE COLOR WORKS, INC.
YORK, PENNSYLVANIA

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to Federal, state, and local agencies; labor; industry and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

HETA 82-326-1420
FEBRUARY 1984
KEYSTONE COLOR WORKS, INC.
YORK, PENNSYLVANIA

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I. Summary

On July 6, 1982, the National Institute for Occupational Safety and Health (NIOSH) received a request for a Health Hazard Evaluation from Keystone Color Works, Inc, York, Pennsylvania. Since 1917, Keystone Color Works has manufactured chemical pigment pulp colors, in which numerous dyes and dye precursors are used; many of which contain aromatic amines which are known or are suspected to be human bladder carcinogens. Eight employees work in the production area of the plant and have extensive exposure to the dyes.

On September 27, 1982, a NIOSH industrial hygienist and medical officer visited Keystone Color Works. All current employees were interviewed, and a walk-through survey of the facility was conducted to observe the production process and employee work practices.

Follow-up medical studies were done on December 15-16, 1982, when NIOSH interviewed two additional employees and obtained urine samples for benzidine and aromatic amine analysis, routine biochemical and microscopic analysis, and cytology. The results of the urine screen showed no detectable levels of benzidine or aromatic amines (less than one part per billion) at the end of a normal work day.

One of the eight production workers was found to have bladder cancer. Three (including the case) of these eight had worked at the plant long enough to have an adequate latency period for the development of cancer following dye exposure (more than 20 years).

On the basis of these results, NIOSH determined that a health hazard existed from exposure to suspected carcinogenic dyes at Keystone. Recommendations to assist current efforts to reduce exposures to dyes, and screen for health effects from past exposure are contained in Section VII of this report.

KEYWORDS: SIC(1) 2865 (Cyclic [coal tar] Crudes, and Cyclic Intermediates, Dyes, and Organic Pigments [Lakes and Toners]); SOC(2) 7664, 7666, 7759; DOT(3) 550.684-014, 550.685-014, 551.685-082; azo dyes, pigment manufacture, dye manufacture, dyes, bladder cancer, urine cytology, cancer screening.

II. INTRODUCTION

On July 6, 1982, the plant manager of Keystone Color Works, York, Pennsylvania, at the suggestion of an Occupational Safety and Health Administration (OSHA) industrial hygienist from the Harrisburg, Pennsylvania office, requested NIOSH to conduct a medical evaluation of Keystone employees. A NIOSH medical officer and industrial hygienist visited the plant on September 27 and 28, 1982. At that time, 11 employees were interviewed, and a walk-through survey of the facility was conducted. On December 15 and 16, 1982, the NIOSH medical officer again visited the plant and conducted additional interviews, and obtained urine samples.

III. BACKGROUND

Keystone Color Works, Inc. is a small dye plant which has been manufacturing a host of dyes and pigments since 1917. The plant has been under its present management since 1932, and at present manufactures a number of diazo dyes and pigments. In the past, the company used benzidine as a raw material (no quantities available). Several of these dyes or dye intermediates used in the current dye/pigment production are known or are suspected to cause bladder cancer in humans (see discussion for listing). The plant employees 13 people; eight of these are in production, two work in a small laboratory, and three are in the office area. The plant is situated in an old three-story building which covers approximately one-half a city block in downtown York.

The upper floor of the three-story building is used for storage of the raw materials and the finished product. The second floor contains a total of 48 300-gallon diazo and solution mixing vats, segregated by color (red, yellow, blue, and green). The bottom floor contains 24 3000-gallon mixing and boiling vats, plus a pulp filter press.

The initial step of the production process is weighing of the dry, raw materials on portable scales located on the second floor of the facility. This operation is normally conducted by one employee during the afternoon so that the materials will be ready for mixing at the start of the shift the following morning. Approximately 120 raw materials are used for the various types of pigments. The employee normally wears a 3M disposable dust mask during weighing.

At the start of the shift, the pre-weighed materials are loaded by hand into the diazo and solution vats and water and acid are added. The mixtures are then heated and allowed to mix for several hours. The contents of the smaller vats are then drained simultaineously into the large vats on the first floor. Steam is injected into the solution for several hours during the mixing. The final product is tested for color match against standards. If the color does not match, dyes (some benzidene based) are added. The pigment is then passed through the filter press and the resulting pulp is packaged in 55-gallon drums for shipment.

Ventilation consists of a number of wall-mounted exhaust fans located throughout the facility. Rubber gloves and half-face organic vapor/acid mist cartridge respirators equipped with pre-filters are used when weighing or hand loading the vats with substances displaying warning labels.

IV. MATERIALS AND METHODS

Medical

All 13 employees at the plant were interviewed concerning their medical, occupational, and chemical exposure histories. In addition, company insurance claims and personnel records of former employees were reviewed. NIOSH also reviewed previous testing for blood lead and urine protoporphyrins.

Urine was collected during the follow-up medical survey at the end of the daily eight-hour work shift in the middle of the work week. Following collection, specimens were transported to a local hospital where approximately 50 milliliters of each urine specimen was centrifuged at 4000 rpm for 10 minutes. The supernatant was discarded and 50 milliliters of Carbowax fixative was added to each pellet. These fixed specimens were utilized for urine cytology. The remaining urine was transported on ice within three hours of collection to a local clinical laboratory where approximately 5 milliliters was used for urinalysis. The remainder of the urine specimens were frozen and transported back to Cincinnati

A pathologist at the University of Pennsylvania, performed the urine cytology examination.

The Benzidine in Urine (Screening Test) Method, P&CAM 315, NIOSH Manual of Analytical Methods, DHEW, Vol. 5, 1979, was used for the determination of both the free aromatic amines and benzidine. Briefly, the aromatic amines, including benzidine congener-based dyes are extracted from urine with chloroform and derivatized with 2,4,6-trinitrobenzene sulfonic acid (TNBS). The chloroform containing the free aromatic amines (TNB-derivative) is quantitated spectrophotometrically at 400 nM using benzidine as a standard. The lower detection limit for the spectrophotometric method is 1 part per billion (ppb) free aromatic amines. The chloroform extract is next concentrated under a gentle stream of nitrogen then benzidine identification is determined by thin-layer chromatography (TLC).

All workers were notified of the results of their tests by letter.

V. EVALUATION CRITERIA

A. Azo Dyes

Azo dyes (4, 5, 6) are the largest and most versatile class of synthetic dyes. This well-defined group of compounds is characterized by the presence of one or more azo groups (-N=N-).

Peter Greiss synthesized the first azo dye soon after his discovery of the diazotization reaction in 1858. The two reactions which form the basis for azo dye chemistry are diazotization and coupling. The diazotization reaction may be stated as:

$ArNH_2 + 2HX + NaNO_2$ yields $ArN_2{+}X^{-} + NaX + 2H_2O$ #1

where X = Cl, Br, NO_3, HSO_4, BF_4, etc. Coupling proceeds according to the equation:

$ArN_2{+}X^{-} + HR$ yields $ArN{=}NR + HX$ #2

where R is a alkyl or aryl. In the dye industry, diazotizations and coupling are carried out in an aqueous medium whenever possible.

Diazotization

Practically every aromatic primary amine is a potential diazo component. Diazotization (5) involves treating a primary aryl amine with nitrous acid to form a diazonium salt as given in equation #1. Sodium nitrite, $NaNO_2$, a mineral acid, such as muriatic acid (aqueous HCl) or dilute sulfuric acid, are used for the diazotization in a majority of cases.

Coupling

The coupling reaction (5) between an aromatic diazo compound and a coupling component is the single most important synthetic route to azo dyes. All coupling components used to prepare azo dyes possess one common feature, an active hydrogen atom bound to a carbon atom. Compounds of the following types can be used as azo coupling components; compounds that possess phenolic hydroxyl groups, such as phenols and naphthols; aromatic amines; and heterocyclic compounds, such as those containing pyrrole, indole, and similar ring systems.

The azo coupling reaction is an electrophilic aromatic substitution. The reaction is facilitated by electron-attracting groups in the diazo component, and by electron-donating groups in the phenol and aromatic amine-type coupler components.

Normally, coupling occurs at the position para to the hydroxyl group. If this is occupied by a substituent not readily eliminated, as in beta-naphthol, the diazo component attacks the ortho position. When both ortho and para positions are free, two aryl azo residues can be introduced. A few well-known coupling components are shown in figure 1 with the favored positions of coupling under the conditions normally used. Generally, phenols couple more readily than amines, and members of the naphthalene series more readily than members of the benzene series.

B. Occupational Bladder Cancer

Occupational exposure to aromatic amines has long been associated with the development of bladder cancer. Rehn reported the first cases in 1895 (7,8). Four of 45 exposed workers employed in the manufacture of the dye fuchsin (magenta) from aniline developed bladder cancer. Due to the rarity of this cancer in the general population at that time, Rehn realized the etiolic significance of his observation.

Subsequent reports confirmed this association (Reviews: 9, 10, 11, 12). Many of these epidemiologic and animal studies focused on the identification of specific carcinogenic dyes. Some of the difficulties encountered in determining the causative agents included (13):

1. Worker exposure to more than one suspect compound, further complicated by workers shifting between departments.

2. Different degrees of exposure hazard between processes.

3. Unsuspected trace amounts of impurities, possibly more harmful than the parent compound.

4. Different compositions of dyes and production methodology in different factories, complicating statistical comparison.

Initially, aniline was felt to be causative; and thus the term "aniline cancer" came into use. Subsequent studies, however, have shown that other intermediates in the dye-making process are the responsible agents and not aniline (14).

Benzidine

Benzidine, also called 4,4'-diaminobiphenyl and p-diaminodiphenyl, is used in the manufacture of azo dyes, where it is diazotized and then coupled with other intermediates to form dyes. Benzidine base and its salts can be absorbed through the skin or by inhalation or ingestion (15). Epidemiologic studies of worker populations exposed to benzidine have demonstrated that the compound and its salts are human bladder carcinogens (16, 17, 18, 19; Reviews 9, 20, 14). The incidence of bladder cancer in benzidine workers exceeds the incidence of the disease in the normal population by a factor of 30 or more. The average induction (latency) period from the first benzidine exposure to the clinical diagnosis of malignancy has been reported as 16 and 18.7 years.[16,17] Due to its toxicity, the Occupational Safety and Health Administration (OSHA) designated benzidine as one of its regulated carcinogens.

In addition to benzidine, a host of dyes and dye intermediates, related chemically to benzidine have been shown to be carcinogenic in humans and/or laboratory animals (21, 7, 22, 23, 15).

2-Naphthalamine

The induction of bladder tumors in workers exposed to 2-naphthalamine (2-NA), also known as beta-naphthalamine, is one of the most well-established cause and effect relationships in occupational medicine (9). Case (16) estimated the risk of bladder cancer in workers exposed to 2-NA to be 61 times greater than that in the general population. The average latency has ranged from 5 to 45 years with an average of 16 ± 6 years. Cancer has been seen in individuals with exposures of less than one year (9). 2-NA is no longer manufactured in the United States and, like benzidine, is one of the OSHA regulated carcinogens.

Animal experiments have also confirmed the carcinogenicity of these dyes in non-human species and provide a valuable method of screening other dyes for potential human carcinogenesis (Table I). In a National Cancer Institute sub-chronic study of rats and mice exposed to benzidine, hepatocellular carcinomas appeared five weeks after initial exposure. This time-to-tumor interval is the shortest ever reported in the Institute's Bioassay Program (22). Many other dyes have been tested in this and other programs, and the results of these tests are summarized in the references (IARC - 11, 24, 25, 12, 26; NTP - 27; RTEC -28).

A short review of the epidemiology of bladder cancer is contained in reference 10. In addition to aromatic amines, cigarette smoking is the other major risk factor for bladder cancer. Of interest, cigarette smoke contains 2-NA (10).

VI. RESULTS AND DISCUSSION

A. Environmental

Observation of the employees and discussions with management revealed that since the investigation by OSHA, work practices have improved dramatically. Also, the use of personal protective devices has significantly decreased the potential for exposure to the process chemicals. However, the intermittent exposures to the benzidene-based dyes or other suspect carcinogens requires a higher level of protection than is currently available. The most appropriate method of protection when working with carcinogens is supplied-air respirators. However, in situations of intermittent exposure combined with labor intensive operations covering relatively large work areas (as is the case with this pigment production facility), alternate forms of respiratory protection may be acceptable. One such alternative is powered air-purifying respirators. Although the "protection factors" of these types of respirators are significantly lower than those of supplied-air respirators, the relative convenience may result in greater acceptance and use, and therefore provide increased overall protection.

B. Medical

The work force of 13 people includes eight who have had significant past and have significant current exposure to the dye-making process. The other five people work in the office or chemistry lab and have no significant exposure to the dyes. Of the eight exposed workers, most have worked at the plant more than 10 years, and two have been there for more than 30 years. Three of these eight have worked at the plant long enough to have an adequate latency period for the development of cancer following dye exposure (more than 20 years). Medical interviews revealed that one of these three workers was diagnosed in 1981 as having a Grade I papillary transitional cell carcinoma of the urinary bladder. The tumor was resected at that time and there has been no recurrence at follow-up visits through summer, 1982. However, at a follow-up visit subsequent to the first NIOSH visit, this worker was found to have recurrent tumor and is currently being treated. No other significant work-related illness was found during interviews with the other workers.

Review of previous lead testing show that blood lead levels ranged from 10-28 ug/dl with a mean of 22.2 ug/dl.

Neither workers nor management appeared aware that several of the raw materials being used at the plant have been shown to be carcinogenic in animals and are considered potential human carcinogens. During interviews, they were informed of the hazard. In addition, NIOSH distributed copies of "Working with Carcinogens", NIOSH Publication 77-206, to all employees.

A review of the list of chemicals used by Keystone revealed that several compounds in current use are carcinogenic in animals:

acid scarlet 2R - CAS 3761-53-3 (25, 28);
basonyl red 481 - CAS 989-38-8 (25, 28);
sodium o-phenylphenate tetrahydrate - CAS 132-27-4 (28);
basic violet 10 - CAS 81-88-9 (25);
acid green 3 - CAS 4680-78-8 (25, 28);
fast scarlet R base - CAS 99-59-2 (27, 24).

In addition, several other compounds in use are currently being tested for carcinogenesis by the National Toxicology Program (28). Finally, due to the large number of dyes in use and the inability to test all of them, there may be other potential carcinogens in use at Keystone Color Works.

No benzidine or aromatic amines were detected (limit of detection: 1 ppb) in current workers at the end of a normal work day. However, in light of the one observed case of bladder cancer and the potential heavy past exposure to the carcinogenic dyes, close surveillance should be maintained on current workers, and former workers should be notified of their potential risk.

VII. RECOMMENDATIONS

In view of the potential exposure of both past and present workers to known or potential carcinogens, and the presence of bladder cancer in one long-term worker, NIOSH recommends the following:

1. Annual screening for bladder cancer, including a symptom history, urinalysis with special emphasis on microhematuria, and urine cytology for all employees. Notification of former workers concerning their exposure and performance of urinalysis and urine cytology.

2. Labelling of chemicals with name, health hazard, and whether the compound is carcinogenic.

3. Instruction of workers in proper handling technique for carcinogens.

4. Approved respirators for situations where engineering controls cannot prevent exposure (already present, but regular maintenance needs to be assured).

5. Change of clothing and shower at end of day (already done).

6. Prohibition of eating, drinking, smoking, and carrying personal objects in the production and laboratory areas. These activities increase the likelihood of inhalation, injestion, and carrying out dyes.

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IX. AUTHORSHIP AND ACKNOWLEDGEMENTS

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X. DISTRIBUTION AND AVAILABILITY OF REPORT

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1. Keystone Color Works, Inc.
2. NIOSH, Region III
3. OSHA, Region III

For the purpose of informing affected employees, copies of this report shall be posted by the employer in a prominent place accessible to the employees for a period of 30 calendar days.

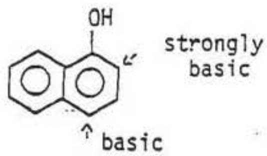
TABLE I*
SPECIES RESPONSE TO CARCINOGENIC EFFECT OF
OCCUPATIONAL BLADDER CARCINOGENS

SPECIES	2-Naphthylamine	1-Naphthylamine	Benzidine	4-Aminobiphenyl
Man	Bladder	Bladder**	Bladder	Bladder
Dog	Bladder	---***	Bladder	Bladder
Monkey	Bladder	---	---	---
Hamsters	Bladder	---	Liver	---
Rat	None	---	Liver, Earduct, Intestines	---
Mouse	Liver	None	Liver	Liver
Rabbit	None	---	---	Bladder

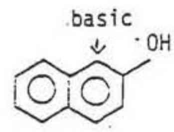
* Taken from Clayson, Reference 11, page 236.
** Contained 4 to 10% 2-naphthylamine.
*** Means not tested

Figure 1*

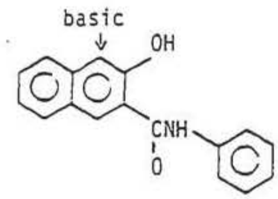
Azo Dye Coupling Components



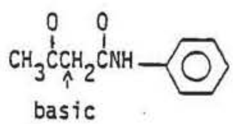
1-napthol



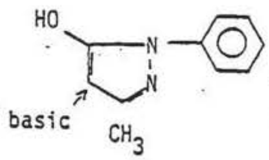
2-naphthol



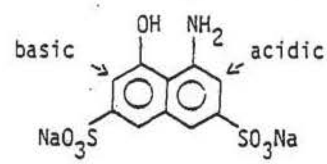
3-hydroxy-2-naphthoic anilide



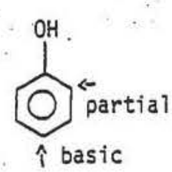
acetoacetanilide



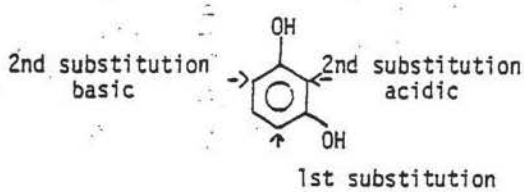
3-methyl-1-phenyl-5-pyrazolone
(enol form)



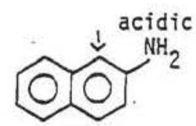
8-amino-1-naphthol-3,6-
disulfonic acid (H acid)



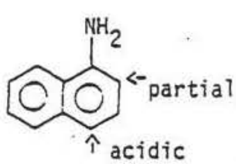
phenol



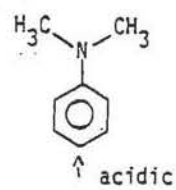
resorcinol



2-naphthylamine



1-naphthylamine



dimethylaniline

Arrows indicate favored positions of coupling under conditions normally used

* From Goheen, Reference 5, pages 388-389.