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Project Summary

Public Health Effects from Industrial Amines Production, A Preliminary Evaluative Approach

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The report gives results of a study to assess the degree to which available data on health effects of chemical exposure, data from the National Cancer Institute, and information on production and use of classes of chemicals suspected of being carcinogenic might be used to identify possible cancer-related operations needing field investigation. The search for exposure intensity data confirmed that such data are not available from the open literature. Although published data are available on national production of some large-volume chemicals, site-specific data on such things as production rates, process losses, and process discharges are almost completely lacking. Until better sources of information are available, studies such as this will have to be supplemented with considerable field investigation to identify specific operations that are suitable for in-depth study. Until some way is established to develop such information so that it can be used with existing health data for identification of potential hazards, kepone and vinyl chloride incidents will continue to be dealt with after considerable damage has already been done. The data analysis techniques presented can be useful in identifying process discharges that must be studied in detail for definition of their potential environmental impact. Volume 2 of the report contains five appendices, including a list of industrial amine chemicals.

This Project Summary was developed by EPA's Industrial Environmental Research Laboratory, Research Triangle Park, NC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

In the last several years the priorities of the U.S. Environmental Protection Agency have shifted to detection and control of human and environmental exposures to toxic emissions containing carcinogenic materials. Chemical analysis and bioassay testing methods are being developed and used as valuable tools in this effort. It seems clear, however, that some systematic but inexpensive approach is needed to set priorities for industries to be investigated and discharge streams to be tested. This is especially true for industries as complex as those involved with the production and use of synthetic organic chemicals.

Because it is felt that production and use of organic chemicals may be in some way relatable to more frequent occurrence of some types of cancer, this project was undertaken. Its purpose is to assess the degree to which available data on health effects of chemical

exposure, data from the National Cancer Institute (NCI), and information on production and use of classes of chemical compounds suspected of being carcinogenic might be used to identify possible cancer-related operations needing further investigation in the field.

Summary

It has been established that industrial usage of certain amine chemicals has in the past resulted in cancer in exposed workers. It also appears that operations involving amine chemicals may be contributing to atmospheric nitrosamines which, according to laboratory animal studies, are highly potent carcinogens Hence industrial practices involving amines were selected for use in this investigation to define how far information in open literature can be used as an inexpensive means of identifying operations that appear to warrant costly characterization studies aimed at full definition of their potential impacts.

The main elements of the investigation were:

1) A master list of over 1900 amine chemicals was developed using the Tariff Commission report on synthetic organic chemical production and the Stanford Research Institute Directory of Chemical Producers. These chemicals were divided into two groups: primary amines, which would not react with NO_x in the atmosphere to form nitrosamines; and secondary or tertiary amines, which could react.
2) Health effects literature was reviewed to identify studies that have been conducted to relate exposure of amines or nitrosamines to the incidence of cancer.
3) Using information from the study of commercial amines and background information from a health effects investigation, 48 amine compounds were identified as candidates for more detailed study. Consideration was given to a) potential toxicity or carcinogenicity of the compound, b) volume of annual production (high volume production was used as an index of possible exposure to humans), and c) potential for reaction to form toxic chemicals.
4) The Stanford Research Institute Directory of Chemical Producers was used to locate sites where one or more of the amines selected for study was being manufactured, and Moody's Industrial Directory was used to identify sites where it could be established that they had been produced for 25 years or longer. No attempt was made to be exhaustive in locating such sites. Investigation of 32 chemicals led to identification of 12 sites. One additional county, where amines have been used in large quantities for many years, was added to make a total of 13 considered suitable for further study.
5) The 13 counties selected were examined to determine:
   a. Whether secondary and tertiary amines capable of being converted to nitrosamines in the atmosphere were included in the population of amines being produced.
   b. Whether organic dyes and pigment in which amines are used were produced in any of the counties.
   c. Whether nitric acid plants, which might contribute to the conversion of amines to nitrosamines in the atmosphere, were present in any of the counties.
6) Data from the National Cancer Institute were used to examine cancer rates in two ways. First, rates of cancer in counties contiguous with those being investigated were compared with rates in the counties of interest. This approach was used to screen out the effect of local conditions (e.g., drinking water) that might be contributing to high incidence of cancer. Second, the absolute values for incidence of cancer were determined for those counties with high relative cancer rates.
7) The relative rates of all 14 kinds of cancer shown in the NCI data base were analyzed, giving special attention to six kinds believed most likely to be associated with amine or nitrosamine exposure (esophagus, stomach, liver, pancreas, kidney, and bladder). In addition the rates of all cancers were compared to provide an index of the general prevalence of cancer from all causes; and the rate for lung cancer, which is the dominant form in terms of frequency, was used as a basis for comparison of frequency of occurrence. A third index, the "relative risk" factor defined by the NCI, was used alon with relative rates and absolut rates to rank the 13 counties Specific results of the rankings ar summarized in Tables 1-4. Table presents the key for numbers an symbols used in the "Cancer pro file comments" column in Table 1-4.
8) Information was assembled o factors that might explain observe cancer rates (relative or absolute) This material included backgroun on population, degree of industri alization, and types of chemica plants in operation in the 13 se lected counties and all surroundin counties. The most notable facto not accounted for was age adjust ment of the cancer rates observed i.e., it was not possible to deter mine whether some of the highe rates could be attributable to gen erally older populations in some counties.
9) Concurrent with the epidemiologi cal analysis, an attempt was made to obtain information on potentia for human exposure to amines o nitrosamines resulting from pro duction or use of chemicals in the selected counties.

Conclusions

The search for data on intensity of exposure confirmed that such information is not available from the open literature. Although published data are available on national production of some large-volume chemicals, site-specific data on such things as production rates, process losses, and process discharges are almost completely lacking. Until better sources of information are available, studies such as this one will have to be supplemented with considerable field investigation to identify specific operations that are suitable for in-depth study. It is doubtful whether data collection authority available to health officials under such legislation as the Clean Air Act and Amendments and the Toxic Substances Control Act is adequate to support the activities needed to document human and environmental impacts associated with the production and use of synthetic organic chemicals. The specificity of the current legislated authority, problems of confidentiality, and other related problems present obstacles that would appear to make systematic development of exposure data difficult. Until some way is established to develop such information so

Table 1. *Relative Rates of All Cancers Versus Selected Cancers in 13 Counties*

All cancers				Selected cancers				Cancer profile comments[a,b]
	Relative rate				Average relative rate			
County, state	M	F	OA	County,state	M	F	OA	
Kanahwa, W. Va.	118	111	114	Kanahwa, W. Va.	140	111	128	(1) (2)
Erie, N.Y.	120	107	114	Erie, N.Y.	125	121	124	(1) (2)
Vigo, Ind.	116	108	112	Vigo, Ind.	119	114	116	(1) (2)
Harris, Tex.	106	108	106	Salem, N.J.	112	110	115	(1) (2)
Warren, N.J.	105	108	106	Washington, Ala.	78	152	97	(2)
St. Clair, Ill.	101	102	102	Harris, Tex.	106	104	104	(1) (2)
Salem, N.J.	98	105	100	Warren, N.J.	99	110	104	(1) (2)
Summit, Ohio	94	97	95	St. Clair, Ill.	96	95	99	(1)
St. Charles, La.	91	99	95	Brazoria, Tex.	92	93	93	
St. Louis, Mo.	91	96	94	Summit, Ohio	92	93	92	
Somerset, N.J.	89	92	91	Somerset, N.J.	88	97	91	
Brazoria, Tex.	87	92	90	St. Louis, Mo.	87	97	90	
Washington, Ala	81	94	87	St. Charles, La.	55	137	72	

M = Male Rate
F = Female Rate
OA = Overall Rate
[a]*Refers to county shown in "Selected cancers" column.*
[b]*See Table 5.*

Table 2. *Absolute Rates of All Cancers and Selected Cancers in 13 Counties*

County, state	All cancers (female)	All cancers (male)	Selected cancers (female)	Selected cancers (male)	Cancer profile comments[a]
Warren, N.J.	147.640^{++}	189.201^{+}	28.242^{+++}	46.198^{+}	(1) (2) (3^{++}) (4^{+++})
Salem, N.J.	146.595^{++}	185.827^{+}	27.133^{++}	54.221^{+++}	(1) (2) (3^{++}) (4^{+++})
Vigo, Ind.	144.191^{++}	180.760^{+}	25.953^{+}	42.105	(1) (2) (3^{++}) (4)
Erie, N.Y.	142.230^{+}	206.966^{+++}	27.454^{++}	56.169^{+++}	(1) (2) (3^{+++}) (4^{+++})
St. Clair, Ill.	138.690^{+}	195.918^{++}	24.060	45.350^{+}	(1) (3^{++})
Summit, Ohio	137.901^{+}	185.488^{+}	25.400^{+}	47.927^{+}	(3^{+}) (4^{+})
Somerset, N.J.	135.655^{+}	182.711^{+}	25.796^{+}	50.384^{++}	(3^{+}) (4^{++})
St. Louis, Mo.	131.979^{+}	181.411^{+}	22.881	42.786	(3^{+})
Kanahwa, W. Va.	126.141	172.278	25.974^{+}	43.605	(1) (2)
Harris, Tex.	124.176	188.483^{+}	22.069	44.348	(1) (2) (3)
Washington, Ala.	114.009	150.645	23.420	36.050	(2)
Brazoria, Tex.	113.951	165.026	21.957	42.923	
St. Charles, La.	112.541	185.710^{+}	27.047^{++}	32.900	(3) (4^{++})

National average: All cancers - 129.974 - female
172.733 - male
Selected cancers - 24.232 - female
44.405 - male

$^{+}$ *Above average.*
$^{++}$ *>10% above average rate.*
$^{+++}$ *>15% above average rate.*
[a] *See Table 5.*

that it can be used with existing health data for identification of potential hazards, "kepone" and "vinyl chloride" incidents will continue to be dealt with after considerable damage has already been done. The data analysis techniques presented here can, however, be useful in identifying process discharges that must be studied in detail for definition of their potential environmental impact. Some specific questions seem to require further county-specific investigations. These include:

(1) What factors make Salem County and Warren County, New Jersey, high in relative rates of cancer, "all cancer" rates, relative risk of selected cancers, and relative risk of bladder cancer despite their low population, population density, and degree of industrialization?

(2) Why is Erie County, New York, highest in cancer rates for all categories studied? Is there a connection between these rates and the known presence of facilities producing and using amines or producing nitrosamine precursors?

(3) What factors make the cancer rates of Summit County, Ohio, high for all cancers, selected cancers, and bladder cancer? (This county was included in the study only because amines are known to be used in rubber processing. No production of amines or nitrosamines has been identified.)

Although other questions are suggested by the assembled data, the absence of evidence to substantiate the exposure of humans to amines or nitrosamines as a result of the investigated

Table 3. *Thirteen-County Ranking Based on Relative Risk of All Cancers*

County, state	Combined average for male, female	Male	Female	Cancer profile comments[b]
Erie, N.Y.	115.1	120.3[a]	109.4[a]	(1) (2) (3^{++}) (4^{+++}) (5^{++})
Warren, N.J.	111.5	109.6[a]	113.8[a]	(1) (2) (3^{++}) (4^{+++}) (5^{++})
St. Clair, Ill.	110.5	114.1[a]	106.5[a]	(1) (3^{++}) (5^{++})
Salem, N.J.	109.9	107.9	112.4[a]	(1) (2) (3^{++}) (4^{+++}) (5^{+})
Vigo, Ind.	106.7	103.9	109.8[a]	(1) (2) (3^{++}) (4) (5^{+})
Summit, Ohio	106.3	106.6[a]	106.0[a]	(3^{+}) (4^{+}) (5^{++})
Somerset, N.J.	104.6	105.2	103.8	(3^{+}) (4^{++}) (5)
St. Louis, Mo.	102.7	104.0[a]	101.4	(3^{+}) (5^{+})
Harris, Tex.	102.8	109.7	95.5	(1) (2) (3) (5)
Kanahwa, W. Va.	99.4	101.0	97.6	(1) (2)
St. Charles, La.	94.3	101.5	85.7	(3) (4^{++})
Brazoria, Tex.	92.8	96.0	88.9	
Washington, Ala.	86.8	86.1	87.7	(2)

[a]*Statistically significant high relative risk, all cancers.*
[b]*See Table 5.*

Table 4. *Thirteen-County Ranking Based on Relative Risk and Adjusted Relative Risk of Bladder Cancer*

County, state	Relative risk male/female	Adjusted relative risk male/female	Cancer profile comments[a]
Salem, N.J.	245.8/155.0	2.28/1.38	(1) (2) (3^{++}) (4^{+++}) (5^{+}) (6^{+})
Erie, N.Y.	147.8/124.7	1.23/1.14	(1) (2) (3^{+++}) (4^{+++}) (5^{++}) (6^{++})
Warren, N.J.	118.1/141.8	1.08/1.25	(1) (2) (3^{++}) (4^{++}) (5^{++}) (6)
Summit, Ohio	118.1/117.1	1.11/1.10	(3^{+}) (4^{+}) (5^{++}) (6^{+})
Somerset, N.J.	113.4/128.5	1.08/1.24	(3^{+}) (4^{++}) (5) (6)
St. Louis, Mo.	112.9/106.6	1.09/1.05	(3^{+}) (5^{+}) (6)
Vigo, Ind.	103.5/120.3	<1/1.10	(1) (2) (3^{++}) (4) (5^{+})
St. Charles, La.	113.4/96.8	1.12/1.13	(3) (4)
Harris, Tex.	106.9/96.1	<1/1.01	(1) (2) (3) (5)
St. Clair, Ill.	93.9/102.8	<1/-1	(1) (3^{++}) (5^{++})
Kanahwa, W. Va.	90.9/96.6	<1/-1	(1) (2)
Washington, Ala.	86.9/48.5	1.01/-1	(2)
Brazoria, Tex.	56.8/95.6	<1/1.08	

[a]*See Table 5.*

industrial activities makes further discussion inappropriate.

As indicated earlier it is felt that the results have confirmed the usefulness of health effects studies and cancer rate data in analysis of potential health impacts associated with the production and use of chemicals. Also the results tend to support certain conclusions as to how such studies should be designed. It appears from the results for bladder cancer studies that it is important to identify a form of cancer that is strongly associated with the chemical(s) being investigated and that the chemical be fairly specific to that form of cancer. The results of the study of selected cancers are similarly interesting from the standpoint of the lack of association with high rates attributed to smoking. It was known however that nitrosamines are "highly versatile"; i.e., apparently capable of producing cancer in animals via any route of exposure and in any organ. It is not surprising, therefore, that selected cancer rates tended to follow all cancer rates and are apparently relatable to general overall cancer rates. This could be because (1) there is a lack of real association of these cancers with nitrosamine exposure, and (2) nitrosamines are so versatile and pervasive in the environment that their impact cannot be distinguished from general contamination that is producing high cancer rates, etc. Whatever the reason, the results demonstrate the importance of selection of cancer forms for studies of the type reported here.

Recommendations

Investigations of possible causes of high bladder cancer rates should be undertaken in Salem County, New Jersey; Warren and Somerset Counties, New Jersey; Erie County, New York; and Summit County, Ohio. The potential of the general population exposure to amines, nitrosamines, or other potentially carcinogenic discharges (e.g., coke oven emissions) should be defined. Such investigations should consider all the industries in the counties named and the discharges from them. Discharges should be tested from facilities that appear the most likely to be causing human exposure to a potential carcinogen and the air and water quality in the vicinity of these facilities should be monitored.

Health records of localities where potentially carcinogenic discharges are believed to be occurring should be studied further (e.g., death certificate information on cases involving bladder cancer should be reviewed to determine

Table 5. Key for Cancer Profile Comments, Tables 1 through 4

(1)	*Above average relative rate, all cancers.*
(2)	*Above average relative rate, selected cancers.*
(3)	*Above average absolute rate, all cancers, male or female.*
(3^{+})	*Above average absolute rate, all cancers, male and female.*
(3^{++})	*More than 10% over absolute rate for all cancers, male, female, or both.*
(3^{+++})	*More than 15% over absolute rate for all cancers, male, female, or both.*
(4)	*Above average absolute rate, selected cancers, male or female.*
(4^{+})	*Above average absolute rate, selected cancers, male, and female.*
(4^{++})	*More than 10% over absolute rate, selected cancers, male, female, or both.*
(4^{+++})	*More than 15% over absolute rate, selected cancers, male, female, or both.*
(5)	*Higher than average relative risk, all cancers.*
(5^{+})	*Significantly high relative risk, all cancers, male or female.*
(5^{++})	*Significantly high relative risk, all cancers, male and female.*
(6)	*Higher than average relative risk for bladder cancer, and adjusted relative risk >1.0, male and female.*
(6^{+})	*Significantly high relative risk for bladder cancer, male or female.*
(6^{++})	*Significantly high relative risk for bladder cancer, male and female.*

whether occupational exposures to amines or nitrosamines might be involved).

The data collection capabilities of the EPA should be examined to see if they are adequate for collection of data to assess the general population exposure to industrial discharges.

Industrial activity and community health should be studied further to evaluate the methodology that has been developed. A study of the possible association between plants producing organic dyes and pigments and the high incidence of bladder cancer might be appropriate.

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***John O. Smith** is the EPA Project Officer (see below).*

The complete reports covered by this Project Summary:

"Public Health Effects from Industrial Amines Production, A Preliminary Evaluative Approach: Volume 1," (Order No. PB 81-129 207; Cost: $12.50, subject to change).

"Public Health Effects from Industrial Amines Production, A Preliminary Evaluative Approach: Volume 2. Appendices," (Order No. PB 81-129 215; Cost: $17.00, subject to change).

The above reports will be available only from:

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