Exposure Indices for Epidemiological Surveillance of Carcinogenic Agents in an Industrial Chemical Environment

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A prospective system for establishing chemical exposure indices was developed and implemented for 22 chemicals used at a Louisville chemical plant. Validation of the indices was done statistically using industry-related cancer (liver angiosarcoma) and worker-matched controls. A rank ordered system for exposures was used to identify a relationship between the occurrence of disease and the presence of a suspect chemical used in the industrial environment.

A major difficulty in the epidemiology of occupational carcinogenesis is obtaining accurate exposure data, especially if the data must be procured after cancer develops. While epidemiological investigations of outbreaks of disease, infectious or chronic, are always retrospective, the long latent period between exposure to a causative factor and the occurrence of cancer complicates this problem. Routine continuous recording of exposure to possible carcinogens is an ideal goal. Unfortunately, this is not practical for most chemicals in a modern industrial setting. What is eminently practical, however, is a system utilizing rank ordering of exposures for highly suspect chemicals.

The B. F. Goodrich Louisville Chemical plant developed such a system in 1974 in response to the discovery of cases of hepatic angiosarcoma.[1-5] This system was the basis of the initial reports. It was extensively modified during a prospective medical screening program established by the University of Louisville under contract NO1-CN-55212 with the cancer control program of the National Cancer Institute.[6,7] The authors are unaware of other similar existing data sets. Occupational studies are usually based on group, rather than individual, exposures. An excellent review of the literature is given by Gamble et al.[8] A recent discussion of a computerized system is given by Kerr.[9]

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The system for establishing exposure indices on an ongoing basis was developed through employee work histories and rank ordered job exposure categories. All jobs are classified uniquely by both area location and work description by means of area-description (A-D) codes which identify employment occurring in a particular building or area, independent of job; in a particular job, independent of building or area; or by both area and description.

The exposure index combines two components, i.e., work history and job exposure category, by utilizing the A-D code. The chemical exposure rating is an ordered, six-category ranking assigned to each A-D number for each calendar year, as follows:

Rating	Level of Exposure
0	Absent from Environment (on leave, furlough, layoff, etc.)
1	Lowest Exposure (includes exposure up to somewhere near one hour per day)
2	Minimal Exposure to Low Levels (chemical in building — not handled; low vapor pressure and dust level; individual probably works on different floor)
3	Moderate Exposure (works around the chemical, but exposure is minimal; individual is frequently exposed to little spills or leaks and infrequently — less than once per month — to large spills or leaks)
4	Works in Area Subject to High Occupational Exposures (normally exposure is minimal, but large spills or leaks occur once per month or more)
5	Works in Areas Where Level is High (exposure levels in area are frequently high; might consider that some risk is involved if the chemical is very toxic)
6	Intimate Contact — Skin or High Inhalation (includes individuals with daily and direct contact with the chemicals, such as poly cleaner in the old days and those who handled slurry)

Reprinted from Journal of Occupational Medicine
May, 1981, Volume 23, No. 5
pp. 353-358

Table 1. — Detailed Work and Exposure History.

	1A Work History			1B Exposure Rank for Each Chemical				
Year	A Building	D Job	No. Months	Vinyl Chloride	2*	3*		22*
1944	000	576	6	2	1	1	....	4
1945	000	576	5	2	1	1	....	4
1945	111	194	7	5	1	1	....	1
1946	111	194	12	6	4	1	....	1
1947	111	194	12	6	4	3	....	1
1948	111	194	8	5	4	3	....	1
1948	121	192	4	4	3	1	....	1
1949	121	192	4	4	3	1	....	1
1949	112	253	8	2	6	3	....	2
1949	112	253	8					
1949	112	253	8					
1949	112	253	8					
1957	121	235	12	4	3	1	....	1
1957	121	235	12					
1957	121	235	12					
1957	121	235	12					
1972	117	573	5	1	2	1	....	1
1972	000	574	7	2	1	1	....	4
1973	000	574	12	2	1	1	....	4
1974	000	574	8	2	1	1	....	4
1974	Terminated							

*Other chemical

Twenty-two chemicals from two distinct manufacturing processes, one related to synthetic rubber and the other to plastics, were selected for rating. The ratings were assigned by panels of chemical exposure judges. The full six-point scale was not utilized for all chemicals. Although it would have been ideal to have a quantitative, continuous scale of actual exposure to parts per million, this was not available for all B. F. Goodrich employees for all chemicals (nor is it likely to be available in any other industry). In order to overcome the subjectivity inherent in this exposure rating system, knowledgeable people from each area of the plant were selected to serve as that area's chemcal exposure judges. The primary criterion for their selection was experience in the given area. As a rule, production foremen and technical people (i.e., chemical engineers) were in the majority among each area's panel of judges. The area production foremen were especially invaluable as they are experienced in and knowledgeable of all jobs performed in their areas. Most valuable, however, were those individuals who had been at the plant since its inception, or shortly thereafter. The chemical exposure judges met as a group and agreement was by consensus.

Table 1A gives the work history for a hypothetical individual. Note that each job is identified for each year indicating both the A-D number and the number of months worked during the year. This individual, therefore, began work in 1944 and worked for six months on A-D number 000576. He worked an additional five months on this number during 1945. He completed the last seven months in 1945 working at A-D number 111194. Table 1B identifies the exposure rating assigned to each of the 22 monitored chemicals for each A-D number for each year. For instance, the first row indicates the exposure ratings assigned in 1944 to A-D number 000576. In 1945 these remained unchanged. The third row indicates the exposure ratings for A-D number 111194 during 1945. The information in Tables 1A and 1B is combined to give cumulative exposure rank months (CERM) and average exposure ranks (AER). In this example, this individual in 1944 would have had 12 CERM for vinyl chloride in 1944, having worked six months at an exposure rank of 2 during the year. During 1945, this individual would have had CERM to vinyl chloride of (5×2) plus (7×5) or 45. He would have worked a total of 12 months and would have had an AER $(45 \div 12)$ equal to 3.75. The assumption is made that the CERM can be used as a rank order statistic. The assumption is empirically validated later in this paper. The CERM cannot be considered as representing interval data and no such use of it is intended. The results given here are based on revised work histories and A-D codes developed during the NCI contract period. These same codes are now applied to the individual monitoring of all employees.

The data are accurately obtained in a prospective manner. Work histories are obtained on an ongoing basis. Each time an employee changes jobs, the change is identified by a payroll change card indicating the last A-D number, the new A-D number and the date of change. In addition, the rating of exposures by A-D number is now done on an annual basis using auxiliary information available about the A-D number including individual and area monitoring pertinent to the particular A-D number. Thus far this is available for only three chemicals and only since 1974. The rating of exposures is now obtained from chemical exposure judges consisting of representatives of both labor and management. This process takes about two weeks annually.

In order to determine whether such a system could work retrospectively, work histories were abstracted by A-D numbers from payroll records for all employees who worked on or after January 1, 1974, from records dating back to the opening of the plant in 1942. Payroll records

Table 2. — Standard Normal Deviates Comparing Exposure Ranks of Angiosarcoma Cases with the Average Exposure of Matched* Controls (by Selected Chemicals).

	Group			
Chemical	1 (23 Controls)	2 (29 Controls)	3 (36 Controls)	4 (4 Controls)
1	−1.43	2.32	−0.66	−2.20
2	−2.13	−0.93	−2.00	−0.53
3	−3.54	−2.16	−3.16	−1.50
4	−3.31	−1.79	−0.06	−1.76
5	3.97	0.84	5.08	1.11
6	−2.01	−2.58	−1.59	—
7	−2.33	−2.59	−1.93	−1.50
8	0.29	−0.47	1.56	—
9	−3.92	−0.27	6.44	−2.28
10	−0.76	3.64	0.17	−0.71
11	11.27	7.59	0.93	5.08
12	−1.69	−1.35	0.45	−1.00
13	−1.78	−1.41	5.95	0.00
14	−2.41	−2.91	−2.35	−0.85
15	−1.87	−1.63	0.40	−1.21
16	5.13	3.12	5.77	2.55
17	−0.77	−3.43	5.53	−1.50
18	1.55	−1.45	5.68	1.07
10	2.56	−4.36	4.64	−0.83
20	9.11	2.65	3.72	2.60
21	−3.87	−2.39	−2.91	−1.31
22	6.55	2.34	2.36	2.85

*Matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974

did not have the A-D numbers that were subsequently developed; these older records referred to many jobs which no longer existed, and to some which were performed in buildings long since torn down. However, a staff of knowledgeable employees matched the jobs listed on these payroll records with current A-D numbers. Final determination for controversial work records was made, wherever possible, by an individual employee's review. The chemical exposure judges, who were assigning ordered rating exposures to A-D numbers for each year, faced these same problems. They used, in addition to their memory, whatever records of chemical processes and procedures that were available. (The company maintains a file on all products ever produced and all processes ever used at the plant.)

This system of determining work exposure data was *validated empirically* in the following manner: The incidence of hepatic angiosarcoma at the B. F. Goodrich plant since January 1, 1974, presented in four subjects. Each of the four subjects was matched by exact year of birth, by sex and race (white or non-white), by exact year of employment, and by continuing employment at the B. F. Goodrich plant through January 1, 1974. All matches are included in the subsequent analysis. Each of the angiosarcoma subjects and the corresponding matched group were compared on CERM separately for each calendar year. The results were then ranked within each calendar year and the ranks were summed over the calendar years. If the work histories and the ordered rating exposures were no better than random assignments, one would expect a uniform distribution of ranks within each year and independence from year to year. Otherwise, rank order exposures should demonstrate higher exposure to vinyl chloride in those individuals with hepatic angiosarcoma.

Table 2, which gives standard normal deviates, was calculated from the observed sum of ranks, the expected sum of ranks, and the theoretical standard error (conditional on the observed pattern of tied ranks) of the expected sum of ranks. Sums were over years. The results show a very clear pattern of high exposure to chemical number 16, vinyl chloride. This is to be expected a priori if the work history data and the exposure rank data are valid. A second finding of importance is that all four angio-

Table 3. — Comparison of Frequency of Observed and Expected Excess Exposure to Selected Chemicals.

Number of Angiosarcomas Showing Excess Exposure	Expected* Proportion	Observed Frequency	Expected Frequency	Contribution to Chi Square
0	1/16	6	1.25	18.05
1	4/16	6	5.00	0.20
2	6/16	2	7.50	4.03
3	4/16	1	5.00	3.20
4	1/16	5	1.25	11.25
Total		20	20.00	36.73 = X_4^2 $p < 0.001$

*Calculated from the binomial distribution with $n=4$ and $p=1/2$

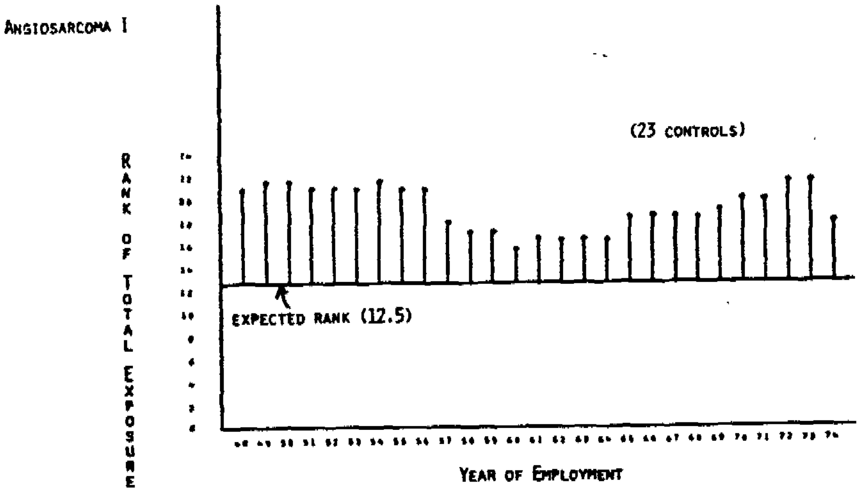

Fig. 1 — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

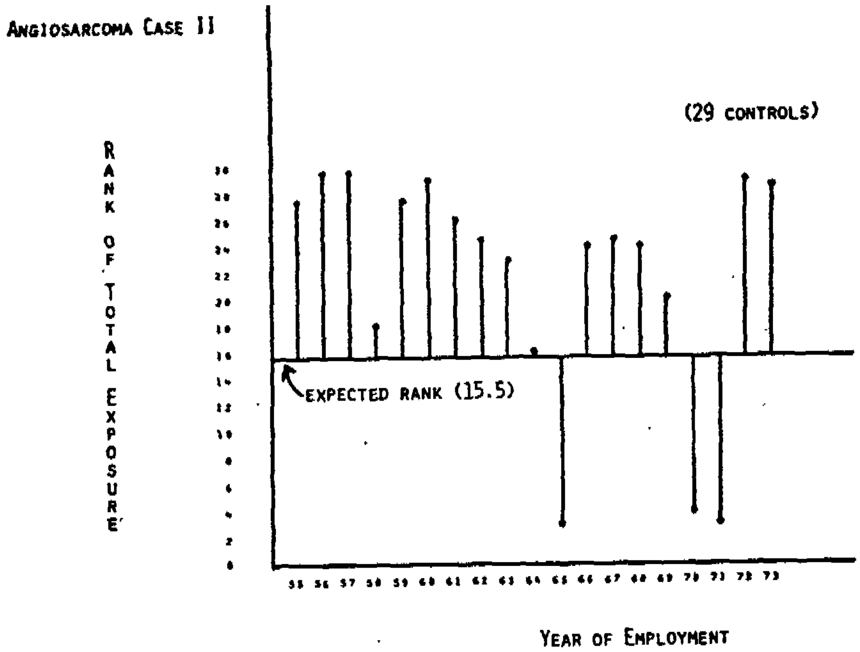

Fig 2. — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

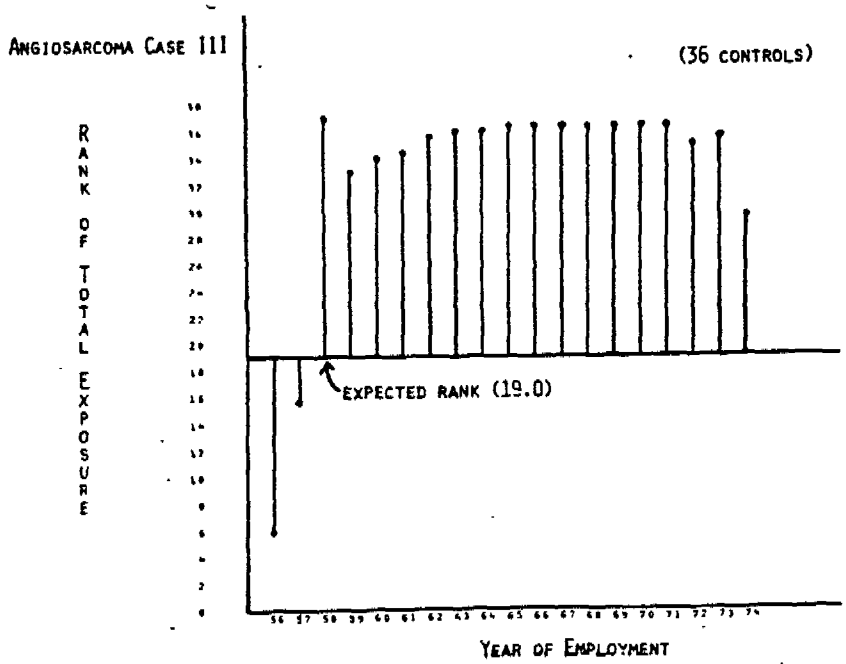

Fig 3. — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

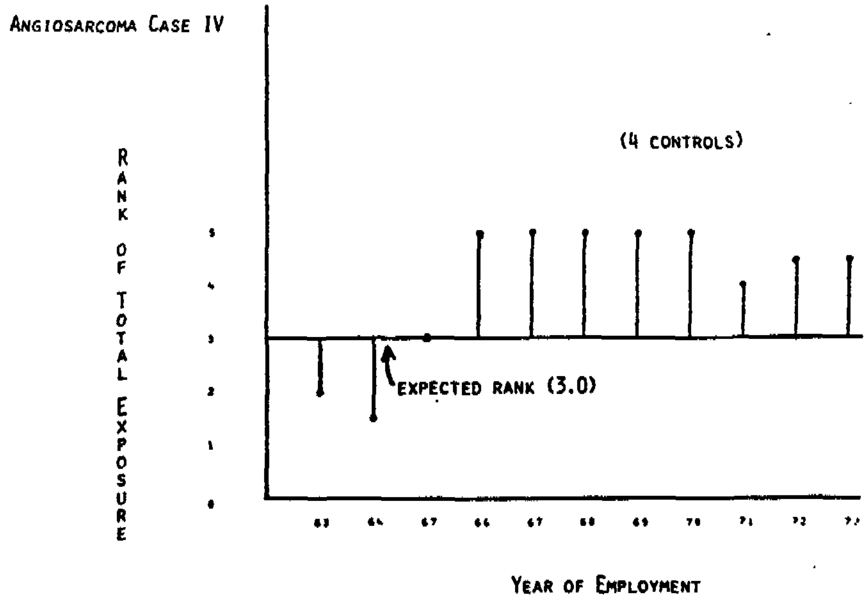

Fig 4. — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

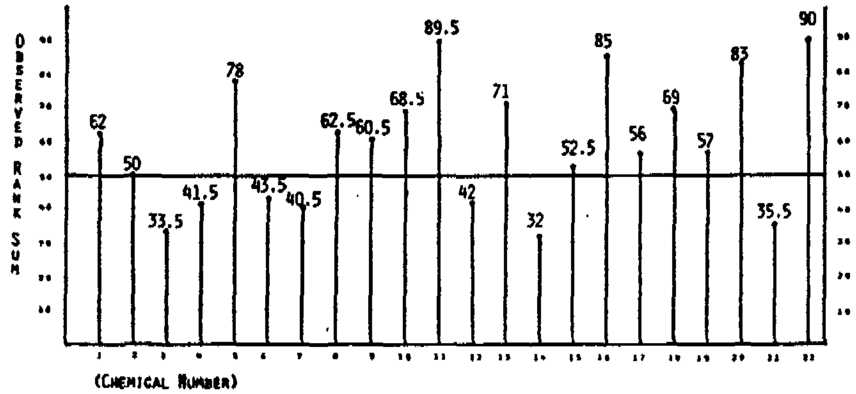

Fig 5. — Observed and expected cumulative exposure rank sums for four angiosarcoma cases compared with matched sets of controls. (Matched by age, sex, race, year of employment and survival as a B. F. Goodrich Chemical Company employee to January 1, 1974. The numbers of controls for the four angiosarcoma patients were 4, 23, 29 and 36. The maximum possible rank sum is 96 and the minimum is 4. Expected rank sum is 50. A rank sum of 80 or more would occur by chance 2.6% of the time. A rank sum of 20 or less would occur 2.6% of the time.)

sarcoma subjects also showed significantly high exposures to chemicals number 20 and 22. Chemical number 20 is a group of catalysts used only with vinyl chloride and chemical number 22 is hexane, used as a solvent for the group of vinyl chloride catalysts. In addition, the data also strongly suggest a high exposure to chemical number 11, diethyl maleate, also a specialized catalyst used only for a specialized process with vinyl chloride.

A clear pattern of exposure is apparent in Table 2. All four angiosarcoma subjects showed excess exposure to 5 of 20 chemicals (numbers 5, 11, 16, 20, 22). By chance, this would be expected to occur for only 1.25 chemicals. All four angiosarcoma subjects also had less than expected exposure to six additional chemicals (numbers 2, 3, 4, 7, 14, 21). The expectation again is only 1.25. When the binomial distribution is inspected (i.e., the distribution of the number of successes in four trials with the probability of success at each trial being one-half), the results are statistically significant ($\chi^2_1 = 36.7$; $p < 0.001$). These are summarized in Table 3. Once more the null hypothesis of random assignment of exposures is rejected. For chemicals number 6 and 8, the exposure was tied for all members of group 4 and they were not included in the analysis. Figs 1 to 4 show the observed to the expected rank exposure for each employee with angiosarcoma by each full year of exposure. The pattern is one of consistent high exposure as compared to the matched controls. It is evident that the system does reflect the autocorrelation in jobs over time as well as the exposure to vinyl chloride among the subjects with angiosarcoma.

To remove the assumption of independence from year to year (as would be required in new field studies), the CERM were summed over years for each angiosarcoma subject and the associated controls. These then provided a single ranking for each matched group. The observed independent ranks of the four angiosarcoma subjects were then summed and compared to the expected rank sums in 5. The exact distribution of the rank sums was obtained by direct enumeration. The angiosarcoma subjects again show significantly high exposure to chemicals number 16 (vinyl chloride), number 20 (catalysts), number 22 (hexane used as a catalyst solvent), and number 11 (diethyl maleate). Fig 6 displays the vinyl chloride rank of the angiosarcoma subject in each matched group; this is the chemical through which empirical validation of the procedure is achieved.

Prior knowledge of the etiology of angiosarcoma was used by the authors to validate these exposure indices. It is questionable what the situation would have been if such prior knowledge had not existed. This study would have shown that employees who subsequently developed angiosarcoma had had high exposure as compared to

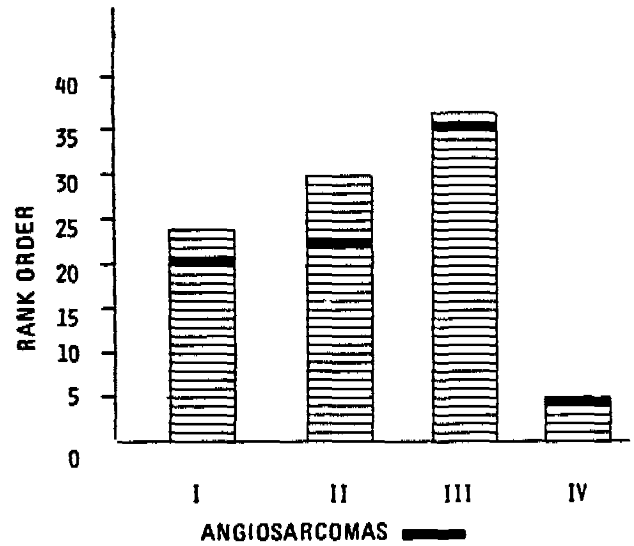

Fig 6. — Vinyl chloride exposure rank of matched individuals with angiosarcoma. (Matched by year of birth, sex, race, year of employment and survival as a B. F. Goodrich Chemical Company employee to January 1, 1974.)

matched controls for a set of four highly correlated chemicals selected from a larger set of 22 studied. These 22 had been selected because of potential toxicity or carcinogenicity by the following criteria: known hepatotoxin, suspected carcinogen, degree of toxicity, degree of contact, and location relative to vinyl monomer polymerization areas. The chemicals would certainly be suspect, but because of correlated exposures, a determination of an exact cause-effect relationship would not be possible. It is certain that further studies would be initiated to interpret the observed events.

The total cost incurred in setting up this system retrospectively (i.e., the cost of going back into records covering plant operation from the beginning up to the present), including the standardization of 321 job classifications ($450), the application of A-D codes to work histories for 1400 employees ($4,760), the assignment of exposure rating to each job classification for each of 35 years for each of 22 chemicals ($880), the extraction of medical history data ($6,000), and computerization ($7,920) was $20,010, or $16 to $17 per employee. The prospective cost, i.e., the cost of work that is recorded regularly forward in time (not including work and exposure history from past times) averaged $3,281 per year, or $2 to $3 per employee, with a breakdown as follows: job classification (1 to 3 new jobs per year), $60; work history (240 new employees per year), $136; exposure indices (20 new chemicals per year), $160; medical data $1,425; and computer costs $1,500. Costs were determined on the basis of actual man-hours worked using industrial hourly wages of the individuals who performed the work.

These data demonstrate empirically that a system of rank ordered individual exposure indices (CERM) for highly suspect chemicals can be implemented in an industrial environment and can identify a known causative relationship between exposure and the development of disease. This system can provide a means of monitoring industrial environments of any size at minimum costs. It can also allow for the introduction of sophisticated monitoring methods and prospective surveillance of an environment, taking into account co-factors which influence biological outcome.

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