analysis of the elongation-termination decision in other prokaryotic and eukaryotic organisms, especially as details of structure and interactions in the elongation complexes of these systems become available.

REFERENCES AND NOTES

1. S. C. Gill, T. D. Yager, P. H. von Hippel, *Biophys. Chem.* **37**, 239 (1990).
2. P. H. von Hippel and T. D. Yager, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 2307 (1991).
3. G. Rhodes and M. J. Chamberlin, *J. Biol. Chem.* **249**, 6675 (1974).
4. K. M. Arndt and M. J. Chamberlin, *J. Mol. Biol.* **213**, 79 (1990).
5. C. Andrews and J. P. Richardson, *J. Biol. Chem.* **260**, 5826 (1985).
6. T. D. Yager and P. H. von Hippel, in Escherichia coli *and* Salmonella typhimurium: *Cellular and Molecular Biology*, F. C. Neidhardt, Ed. (American Society of Microbiology, Washington, DC, 1987), pp. 1241–1275.
7. ———, *Biochemistry* **30**, 1097 (1991).
8. G. A. Rice, C. M. Kane, M. J. Chamberlin, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 4245 (1991).
9. F. H. Martin and I. Tinoco, Jr., *Nucleic Acids Res.* **8**, 2295 (1980).
10. X. Yang and J. W. Roberts, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 5301 (1989).
11. W. A. Whelan and A. Das, unpublished results.
12. W. D. Morgan, D. G. Bear, P. H. von Hippel, *J. Biol. Chem.* **258**, 9565 (1983).
13. D. Jin, R. R. Burgess, J. P. Richardson, C. Gross, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
14. C. A. Brennan, A. J. Dombroski, T. Platt, *Cell* **48**, 945 (1987).
15. T. D. Yager, J. Korte, P. H. von Hippel, unpublished data.

16. We thank many colleagues for discussions and A. Das, C. Gross, and D. Jin for providing unpublished information. Supported in part by USPHS research grants GM-15792 and GM-29158 (to P.H.v.H.) and by a grant to the University of Oregon from the Lucille P. Markey Charitable Trust. P.H.v.H. is an American Cancer Society Research Professor of Chemistry.

Valuing the Health Benefits of Clean Air

JANE V. HALL, ARTHUR M. WINER, MICHAEL T. KLEINMAN, FREDERICK W. LURMANN, VICTOR BRAJER, STEVEN D. COLOME

An assessment of health effects due to ozone and particulate matter (PM_{10}) suggests that each of the 12 million residents of the South Coast Air Basin of California experiences ozone-related symptoms on an average of up to 17 days each year and faces an increased risk of death in any year of 1/10,000 as a result of elevated PM_{10} exposure. The estimated annual economic value of avoiding these effects is nearly $10 billion. Attaining air pollution standards may save 1600 lives a year in the region.

IN THE SOUTH COAST AIR BASIN OF CALIFORNIA (THE BASIN), air quality remains the worst in the nation with respect to particulate matter (PM_{10}), ozone (O_3), and nitrogen dioxide (NO_2). Attaining national ambient air quality standards (NAAQS) (*1*) in the basin will require pervasive, technology-forcing emission controls in addition to changes in life-style. Efforts to determine whether these controls are worthwhile depend on studies that estimate how much health is affected and the value of avoiding these effects.

Executive Order 12291 signed by President Reagan in 1981 requires benefit-cost comparisons for new federal rules, including air quality regulations. The impetus behind this approach—determining how to use limited dollars to provide the greatest good—has led regional governments to pose questions about the worth of pollution-control programs. Estimating the level of benefits resulting from NAAQS attainment is a crucial part of this equation, but remains the more challenging task.

Our approach and resulting estimates of health benefits are somewhat different from those in earlier studies (*2–4*). For O_3-related effects, we included different symptoms from those of earlier workers, assumed that 8 parts per hundred million (pphm) over a 1-hour period was the threshold for O_3-related effects, used more clinical data to derive and validate dose-response functions, and used a fuller characterization of population exposure and dose. For PM_{10}, the major difference is the value of life used to estimate dollar benefits. In the absence of any clear evidence on the age distribution of premature deaths, we used a value from the middle of the generally accepted range rather than the low end.

J. V. Hall and V. Brajer are in the Department of Economics, California State University, Fullerton, CA 92634. A. M. Winer is in the Environmental Science and Engineering Program, Department of Environmental Health Sciences, School of Public Health, University of California, Los Angeles, CA 90024. M. T. Kleinman is in the Department of Community and Environmental Medicine, Air Pollution Health Effects Laboratory, University of California, Irvine, CA 92715. F. W. Lurmann is with Sonoma Technology, Incorporated, Santa Rosa, CA 95403. S. D. Colome is with Integrated Environmental Services, Irvine, CA 92715.

Exposure and Dose Estimation

To generate useful estimates, human exposure modeling must effectively capture exposure and dose received by the entire population (*5*). This process can be difficult but is important because people's susceptibility to health effects varies according to their age and the kinds and times of their activities.

We characterized exposure and dose as fully as possible with the Regional Human Exposure (REHEX) model (*6*), which estimates a population's typical outdoor, indoor, and in-vehicle exposures (*7*) by time of day. Critical to this model is a statistical estimation of the basin population's spectrum of time-activity patterns (*8*).

For each of nine demographic groups, we generated approximately 1000 time-activity patterns (*9*) consisting of typical 15-min intervals spent in a series of microenvironments where pollution levels remained spatially uniform (*5*). We then subdivided each demographic group into time-activity cohorts that followed specific patterns and, using distributions from epidemiological and transportation time-use studies (*10*), estimated an expected frequency of occurrence for each of these patterns. We estimated the concentrations of pollutants to which each group was exposed by dividing the basin into 32 districts corresponding to the ambient air monitoring network of the South Coast Air Quality Management District (SCAQMD). Because of the severity and pervasiveness of NAAQS violations for O_3 and PM_{10} in the basin, we concentrated on these compounds. Hourly O_3 data and 24-hour-average PM_{10} data were used. Limited simultaneous indoor and outdoor measurements were used to determine levels of indoor O_3 resulting from penetration of

Table 1. Prediction equations for O_3-produced symptoms (percentage of individuals exhibiting symptom per unit of dose or exposure). Data derived from (*20, 24*). *D* is the dose delivered to lung expressed in micrograms of O_3. *E* is the maximum 1-hour exposure to O_3 concentration in parts per million.

Symptom	Dose- or exposure-response relation
Sore throat	$14.66 + 0.0246\,D$
Mild cough	$5.25 + 0.0170\,D$
Headache	$4.96 + 0.0150\,D$
Chest discomfort	$-0.64 + 0.0090\,D$
Eye irritation	$-8.63 + 85.453\,E$

outdoor air. Similarly, in the absence of cigarette smoke, indoor concentrations of PM_{10} were primarily due to infiltration rather than to indoor sources. We thus estimated indoor concentrations by applying mean indoor-outdoor concentration ratios of 0.5 and 0.7 (*11*) to the outdoor data for O_3 and PM_{10}, respectively. On the basis of more limited data (*12*), we selected in-transit to outdoor concentration ratios of 0.2 and 1.0 for O_3 and PM_{10}, respectively. Low concentrations of O_3 occur near and in vehicles because the nitric oxide in exhaust rapidly scavenges O_3.

We estimated human dose rates for five ventilation rates (asleep; awake at rest; and low, medium, and high exercise states) using a model of pollutant uptake in the upper and lower respiratory tracts (*13*). We then estimated the portion of each demographic group at each ventilation rate for each microenvironment and hour of the day (*14*).

Estimates of health effects resulting from exposure require knowledge of the mass of pollutant reaching sensitive tissues. For O_3, the sensitive tissues we modeled are the airways of the thoracic sections of the respiratory tract and the eyes.

Relations Among Dose, Exposure, and Response

Because monetary values have been estimated for cough, headache, chest discomfort, sore throat, and eye irritation (*15–17*), we derived dose- and exposure-response relations for these O_3-related symptoms. A few clinical studies have reported individual symptoms at multiple dose levels (*18, 19*), although none have reported all five of these symptoms.

Epidemiological evidence, from several Japanese studies compiled by Imai (*20*), demonstrated that for adults exposed for 1 hour at rest to 8 and 20 pphm of O_3, thoracic doses were 0.4 and 1.6 $\mu g\ kg^{-1}$, respectively. We linearly extrapolated the data from the epidemiological studies to the range of the clinical studies (7.1 to 42.9 $\mu g\ kg^{-1}$) (*18, 19*) and found that these predicted responses were within the range of the clinical data. Because eye irritation arises from external exposure, we plotted these epidemiological data against total oxidant, which consists principally of O_3, concentrations rather than inhaled dose (*21*). The resulting extrapolation of the percent of population reporting eye irritation as a function of oxidant exposure in Japan was in excellent agreement with results from a survey of nurses living in Southern California (*22, 23*).

We used these linearized dose-response results (Table 1) to evaluate the change in percent population reporting symptoms that would occur, given present air quality levels and NAAQS attainment levels. We attributed a threshold function to each symptom, such that no O_3-related health effects were accumulated for doses of less than 8 pphm. Although this cutoff point may be reasonable, recent data indicate that pulmonary function changes and symptoms do occur at this concentration level (*25*); thus, there may be no threshold for O_3 effects.

In contrast to O_3, which produces respiratory symptoms, increased PM_{10} levels are strongly associated with a constellation of systemic effects including increased mortality (*26*). We estimated PM_{10} exposures only from ambient data because we inferred PM_{10}-related effects on the basis of epidemiological studies that relied on ambient measurements. The relation between ambient measurements and dose was assumed to be the same in the basin as in the locations where those studies were conducted. Epidemiological studies cannot prove causality, and because PM_{10} is a complex pollutant, it may be a surrogate measure for one of its components or for another pollutant. Schwartz and Marcus (*27*) have recently shown that the mortality-related particulate effect is independent of sulfur dioxide concentrations, however. Because we did not ascribe mortality effects to any other pollutant, the extent to which PM_{10} is either active or a surrogate would not represent a significant confounding effect, especially in an air basin only in attainment for lead.

To estimate annual occurrences, we used results of Evans *et al.* (*28*), who reanalyzed data from Lave and Seskin (*26*) while controlling for confounding variables. Assuming that the PM_{10} portion of total suspended particulate matter (TSP) is responsible for mortality, we related health effects to PM_{10} level using the observation that on average in California the PM_{10} levels are 55% of the TSP mass (*29*). The relation is PM_{10}-related annual deaths per 100,000 population equals 0.615 times the annual average PM_{10} level in parts per million. Evans *et al.* (*28*) concluded that this relation is as likely an underestimate as an overestimate because noncausal variables related to air pollution are included in some models and are antagonistic to the impact of confounding variables. Because evidence suggests that the exposure-response curve is steeper at lower particulate levels—possibly because of averting behavior at higher concentrations (*27*)—the relation we used is perhaps conservative.

Several studies have reported an association between O_3 levels and minor restricted activity days (MRADs), days on which activity is reduced, but not severely restricted (*30*). The relation we used is $M_j = 0.077\ O_{ij}\ P_j$, where M_j is the change in the number of MRADs for population j on day i, O_{ij} is the change in the daily high O_3 level for a 1-hour period in parts per million on day i for population j, and P_j is population in demographic group j.

A restricted activity day (RAD) includes days missed from work, spent in bed, or otherwise measurably constrained. Ostro (*31*) estimated that the annual number of fine particle–related RADs per person equals 0.0048 times annual average non-PM_{10}–related RADs times annual average fine particle levels in parts per million (where fine particles are those with diameters ≤ 2.5 μm). On average, fine particle concentrations are about 61% of PM_{10} concentrations (*32*); therefore, the relation simplifies to PM_{10}-related

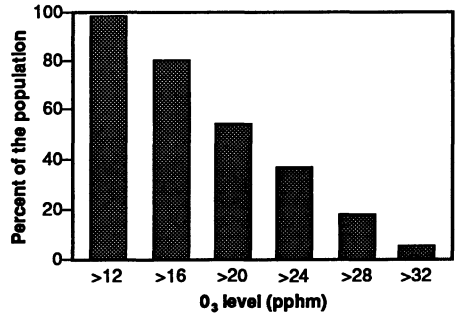

Fig. 1. Percentage of population exposed one or more times per year to various 1-hour O_3 levels. (The 1-hour NAAQS is 12 pphm).

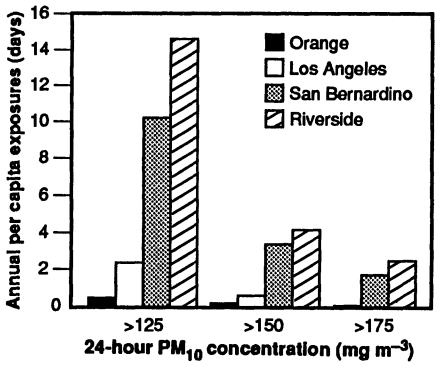

Fig. 2. Annual per capita PM_{10} exposure levels above 125, 150, and 175 μg m^{-3} in each of four counties. (The annual average standard is 50 mg/m^3.)

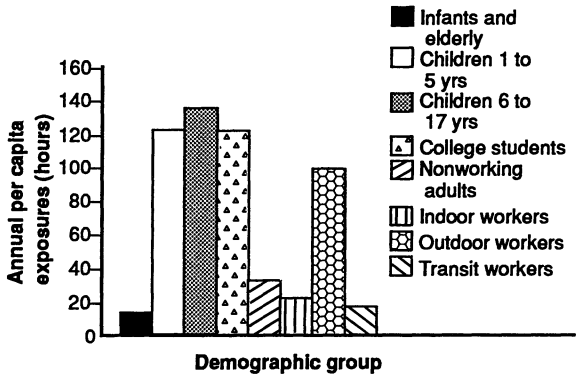

Fig. 3. Annual per capita hours of O_3 exposure above the 12 pphm NAAQS for each demographic group.

RADs per person equals 0.0556 times the annual average PM_{10} concentration. This equation was used to estimate the occurrence of RADs.

Economic Valuation

The value individuals place on reducing the occurrence of specific health effects, from the most severe—risk of premature death—to relatively minor symptoms such as eye irritation, may derive from medical costs and work loss, discomfort, inconvenience, fear, and impacts on others. We valued pollution-related health effects using three economic measures: cost of illness (COI), willingness to pay (WTP), and willingness to accept (WTA). COI measures were calculated from data on wage levels. WTP and WTA measures were derived from hedonic and averting behavior studies, which observe behavior and estimate values from the economic consequences, and from contingent valuation (CV) studies, which survey a sample of the population to elicit the value of nonmarket goods. To determine which measures to use, we gave preference to data that included both direct and indirect costs and to data derived from more than one type of study.

Results. The occurrence of O_3- and PM_{10}-related health effects was calculated by applying the dose-response functions to the distribution of exposure and dose generated by the REHEX model. The results show that large numbers of people in the basin are exposed to high O_3 and PM_{10} concentrations (Fig. 1) and that symptoms related to O_3 occur more often than effects associated with PM_{10}. The PM_{10} estimates indicate that approximately 10 million daily exposures to concentrations in excess of the 24-hour NAAQS of 150 μg m^{-3} occurred per year, slightly less than one per capita (Fig. 2).

Overall, the O_3 and PM_{10} exposure patterns correspond closely to the ambient concentration patterns; however, children, college students, and outdoor workers receive a disproportionately large share of the high concentration exposures, primarily because people in those groups spend relatively more time outdoors (Fig. 3). The model shows that time spent indoors and in vehicles significantly lowers population exposures to O_3 (Table 2).

Although more than 90% of the residents of all counties received O_3 exposures above the NAAQS, geographic differences do occur. For example, 7% of Orange County residents as compared to 30% of San Bernardino County residents were exposed to O_3 above 28 pphm. The predicted reduction of O_3-related symptoms through NAAQS attainment varied greatly with geographic location and demographic group. Among groups, the greatest reductions are predicted for school-aged children and toddlers.

Basin-wide, O_3-related occurrences of cough were estimated to decrease by about 120 million days annually after attainment, or 11 fewer days per capita. Analogous results for the other symptoms are 190 million fewer days of eye irritation (16 per capita); 180 millions fewer days of sore throat (17 per capita); 120 million fewer days of headache (10 per capita); and 65 million fewer days of chest discomfort (5 per capita) (Table 3). Also, O_3-related MRADs decrease by nearly 18 million days annually, or 1.5 per capita.

Although effects related to PM_{10} exposure occur less frequently, they are more serious. Attainment of the federal PM_{10} standard is estimated to result in almost 15 million fewer RADs each year, or 1.2 per capita. Premature death is the most serious, and least frequent, of all effects related to any air pollutant. However, given a population in the basin of more than 12 million in 1990, even effects having small probabilities of occurrence can represent significant numbers of events. We estimate that attaining the standard will prevent approximately 1600 annual deaths attributable to PM_{10} levels. For averted mortality, it is not appropriate to view average effects per individual as simple per capita events. Rather, the average per-person measure actually captures the average reduced risk across the total population. Thus, the average annual risk of death is 1 in 10,000 greater than it would be if the federal annual average standard were attained. To place this result in perspective, in California in 1987, the risk of death in a motor vehicle accident was 2 in 10,000; nationwide, the risk of job-related death was 0.5 in 10,000 (*33*).

Table 2. Comparison of basinwide O_3 exposure with and without microenvironmental factors accounting for indoor and in-vehicle penetration of outdoor ambient air. The 1-hour NAAQS is 12 pphm. Occurrences are numbers of person-days.

O_3 (pphm)	Millions of persons exposed		Millions of occurrences per year	
	With factors	Without factors	With factors	Without factors
> 0	12.09	12.09	103,800.0	103,800.0
> 5	12.09	12.09	6,580.0	13,940.0
> 9	12.05	12.09	1,409.0	4,995.0
>12	11.83	12.09	658.0	2,412.0
>15	10.01	12.09	282.0	1,117.0
>20	6.56	11.70	67.1	280.0
>25	3.68	9.54	14.4	64.4
>30	1.15	3.59	2.5	10.3
>35	0.31	1.00	0.5	1.7

Table 3. Reduction in number of O_3-related symptom occurrences (annual) by county (in thousands).

Symptom	Basin	County			
		Los Angeles	Orange	Riverside	San Bernardino
Cough	121,756	79,286	18,501	9,213	14,756
Headache	107,432	69,958	16,325	8,129	13,020
Eye irritation	191,615	124,070	15,876	17,568	34,100
Sore throat	179,053	116,597	27,208	13,549	21,699
Chest congestion	64,459	41,975	9,795	4,878	7,812
MRAD	17,652	11,669	2,789	1,264	1,929
MMSD	121,756	79,286	18,501	9,213	14,756

Dollar Benefits

Estimates of reduced symptoms and deaths deferred are interesting in themselves but cannot form the basis for comparison between the relative merits of competing social needs. It is therefore important to convert these results into monetary terms.

For reduction of MRADs, the five single symptoms, an intersecting set of symptoms (Table 4), and the value of a statistical life we developed ranges of unit values. One value was developed for RADs (*34*). We adjusted values for multiple occurrences because multiplying the benefits of a 1-day reduction by the predicted number of symptom-days per capita could overstate the WTP to reduce, say, 24 days of an effect (*36, 37*) (Table 5). In many cases, the unadjusted value is over four times the adjusted value. The effect of the adjustment (Table 5) reflects the influence of frequent and severe violations of the NAAQS in the basin compared with those of other nonattainment areas.

The value of avoiding an MRAD should logically exceed the value of avoiding any single symptom, but not necessarily the value of avoiding a severe symptom or a combination of symptoms. Thus, we selected cough—the lowest valued severe symptom (*15*)—as the basis for the low value of an MRAD. We assumed that a day spent suffering from a severe symptom would be highly correlated with at least some restriction in activity and that the value of avoiding a severe symptom would therefore closely approximate the value of reducing an MRAD. Human clinical studies suggest that more than one type of symptom—upper respiratory difficulty and eye irritation, for example—may occur during a single day (*24*). We account for this possibility by terming these multiple minor symptoms days (MMSDs) to avoid overvaluing their joint occurrence. On the basis of the value of multiple symptoms in (*17*), we developed low, mid, and high MMSD values (Table 5).

Because we do not know the distribution of ages in the group that will live longer if the air is cleaner, we cannot assess the value to any one individual of averting death. Instead, we must estimate the value of a statistical life. In effect, this value equals the sum that a group is willing to pay to reduce each individual's risk of death by a small amount. We selected values of \$1.8, \$4.0, and \$9.2 million (in 1990 dollars) per statistical life for low, mid, and high cases, respectively (*38*). The value of \$1.8 million was the lowest supported by empirical work (*39*). According to Viscusi (*40*), \$4.0 million represents both the lower end of the range of values attached to involuntary exposure of the public to small environmental risks and a reasonable estimate of the representative worker's value of life from wage-risk and CV studies. Finally, \$9.2 million was both at the upper range of the values presented by Viscusi and well within the range supported by wage-risk studies (*41*).

Table 4. Average values for MRADs, MMSDs, and symptoms in 1990 dollars.

Effect	Value		
	Low	Mid	High
Cough	\$1.75	\$4.75	\$14.00
Headache	3.00	8.00	22.00
Eye irritation	3.00	7.00	16.25
Sore throat	3.75	8.00	16.75
Chest congestion	3.50	7.50	16.00

Implications

On the basis of our analysis, the basin-wide health benefits of meeting the NAAQS for O_3 are \$1.2 billion to \$5.8 billion, with a best estimate of \$2.7 billion. This estimate incorporates reductions in O_3-related symptom occurrences, including MRADs, MMSDs, and all single-symptom days outside the intersecting set of symptoms represented by MMSDs.

Because society places great value on reducing even a small risk of premature death, the values for attaining the PM_{10} NAAQS are large. Annual dollar benefits range from \$2.9 billion to \$14.9 billion, with a best estimate of \$6.4 billion. Although mortality values dominate, the benefits of reduced RADs are also large in an absolute sense. We estimated that the annual basin value for reducing this effect is more than \$775 million. The total annual value of attaining the federal O_3 and PM_{10} standards ranges from \$5.0 billion to \$21.5 billion, with a best estimate of \$9.8 billion.

These numbers are in part congruent with earlier studies, but generally larger. For example, our estimates of O_3-related benefits are higher than in another study of the basin (*4*) because we modeled dose-response relations and considered the value of exposures over 8 pphm rather than set a threshold at 12 pphm. As a result we estimate that attainment of NAAQS will result in 11 fewer days per capita of cough, in contrast to 2.5 (*4*). PM_{10} benefits in this

Table 5. Adjusted values for symptoms in 1990 dollars.

Effect	Value		
	Low	Mid	High
Cough	\$ 0.50	\$ 1.50	\$ 4.50
Headache	1.00	2.75	7.25
Eye irritation	0.75	1.75	4.00
Sore throat	1.00	2.00	4.25
Chest congestion	1.50	3.25	6.75
MRAD	14.50	23.00	37.25
MMSD	7.50	16.75	37.25
RAD		53.00	

study were calculated using a mid-range value from the literature rather than a low value (*4*). A mid-value is appropriate in the absence of clear evidence that the elderly are the only cohort at risk of premature death and that the elderly place a different value on additional life. Also, we make no benefit-cost comparisons because there is no comparable figure for costs. [For reference, the maximum cost cited in any study was $13 billion (*4*).] Attainment of the O_3 and PM_{10} NAAQS requires control of both NO_x and volatile organic compounds (VOCs), but these controls will lead simultaneously to attainment of the NO_2 NAAQS, improved visibility, reduced greenhouse gases, and reduced ecosystem effects. Ascribing all control costs to O_3 and PM_{10} overstates the costs of meeting those NAAQS standards, yet economists have no accepted method to allocate costs when more than one objective is achieved by an action (*42*).

These various estimates have several implications. One is that benefit estimation has not reached the maturity that policy-makers would like and cannot yet provide definitive answers to difficult economic questions. A great deal is not included; for example, in this study no value is ascribed to improvements in visibility, protection of materials or vegetation, or prevention of chronic lung disease. This work, and that of others (*2–4*), however, shows that some progress is being made and that the foundations for such analyses are becoming stronger. As more comprehensive and accurate health data and better exposure data become available, more effects can be reliably evaluated. Continuing work on valuing reduced risk to life narrows uncertainty. More robust exposure models are needed, and so on. Some questions are inherently political; although we settle on a mid-range value of life, a broader range is provided, reflecting our belief that the political process must decide which value is appropriate. Finally, available information shows that important benefits (including preservation of lung function) are not yet quantifiable in dollars and that current benefit estimates are therefore likely to be underestimates. We conclude that it is prudent to continue pursuing a policy of attainment for the O_3 and PM_{10} NAAQS in Southern California.

REFERENCES AND NOTES

1. The 1-hour O_3 NAAQS is 12 pphm, not to be exceeded more than once a year. For PM_{10}, the 24-hour NAAQS is 150 $\mu g\ m^{-3}$. The annual average NAAQS is 50 $\mu g\ m^{-3}$ for PM_{10}, and 5.34 pphm for NO_2.
2. A. M. Freeman, *Air and Water Pollution Control: A Benefit-Cost Assessment* (Wiley, New York, 1982).
3. A. J. Krupnick and R. J. Kopp, *The Health and Agricultural Benefits of Reductions in Ambient Ozone in the United States* (Office of Technology Assessment, Washington, DC, 1989).
4. A. J. Krupnick and P. R. Portney, *Science* **252**, 522 (1991).
5. K. Sexton and P. B. Ryan, in *Air Pollution, the Automobile and Public Health*, A. Y. Watson, R. R. Bates, D. Kennedy, Eds. (National Academy Press, Washington, DC, 1988), pp. 207–238.
6. A. M. Winer, F. W. Lurmann, L. A. Coyner, S. D. Colome, M. Poe, *Characterization of Air Pollutant Exposures in the South Coast Air Basin: Application of a New Regional Human Exposure (REHEX) Model* (South Coast Air Quality Management District, El Monte, CA, 1989); F. W. Lurmann, A. M. Winer, S. D. Colome, paper presented at conference on Total Exposure Assessment Methodology: A New Horizon, Las Vegas, NV, 27 to 30 November 1989 (U.S. Environmental Protection Agency and Air and Waste Management Association, Las Vegas, NV, 1989); F. W. Lurmann, A. M. Winer, M. Poe, T. Durbin, *Sensitivity Analysis of the Regional Human Exposure (REHEX) Model* (*STI 99170-992-FR*, U.S. Environmental Protection Agency, Santa Rosa, CA, 1989).
7. W. R. Ott, *Environ. Sci. Technol.* **19**, 880 (1985); R. A. Paul, T. Johnson, A. Pope, A. Ferdo, W. F. Biller, *National Estimates of Exposure to Ozone under Alternative National Standards* (*Rep. 68-02-4309/WA32*, U.S. Environmental Protection Agency, Washington, DC, 1986); S. R. Hayes, *J. Air Pollut. Control Assoc.* **39**, 1453 (1989).
8. W. R. Ott, D. Mage, L. Wallace, *Atmos. Environ.* **22**, 2101 (1988).
9. The demographic groups are: children under 1 year of age, children 6 to 17 years old, college students, nonworking adults 18 to 67 years old, adults working predominantly outdoors, adults working predominantly in transit, and adults over 64 years old.
10. M. Schwab, S. D. Colome, J. D. Spengler, P. B. Ryan, I. H. Billik, *Toxicol. Ind. Health* **6**, 517 (1990); D. Klinger and J. R. Kuzmak, *Personal Travel in the United States, 1983–84 Nationwide Personal Transportation Study* (U.S. Department of Transportation, Washington, DC, November 1986); J. Thomas and J. Behar, in *Proceedings of the Research Planning Conference on Human Activity Patterns*, Las Vegas, NV, 8 to 10 May 1988, T. H. Starks, Ed. (*600/4-89-004*, U.S. Environmental Protection Agency, Las Vegas, NV, 1988); A. Szalai, *The Use of Time: Daily Activities of Urban and Suburban Populations in Twelve Countries* (Mouton, The Hague, 1972).
11. C. J. Weschler, H. C. Shields, D. V. Naik, *J. Air Pollut. Control Assoc.* **39**, 1562 (1989); R. H. Sabersky, D. A. Sinema, F. H. Shair, *Environ. Sci. Technol.* **7**, 347 (1973); F. H. Shair and K. L. Heitner, *ibid.* **8**, 444 (1974); W. W. Nazaroff and G. R. Cass, *ibid.* **20**, 924 (1986); J. R. Druzik, M. S. Adams, C. Tiller, G. R. Cass, *Atmos. Environ.* **24**, 1813 (1990); D. Dockery and J. D. Spengler, *J. Air Pollut. Control Assoc.* **31**, 153 (1981); S. D. Colome, J. D. Spengler, S. McCarthy, *Environ. Int.* **8**, 197 (1982).
12. C. C. Chan, H. Ozkaynak, J. D. Spengler, L. Sheldon, paper presented at the Total Exposure Assessment Methodology Conference, Las Vegas, NV, 27 to 30 November 1989; C. L. Green *et al.*, *In-vehicle Air Toxics Characterization Study in the South Coast Air Basin* (Draft Report, South Coast Air Quality Management District, El Monte, CA, 1988); P. E. Baker *et al.*, paper presented at the Air Pollution Control Association Specialty Conference on Combustion Processes and the Quality of the Indoor Environment, Niagara, NY, 26 to 28 September 1988.
13. M. T. Kleinman, S. D. Colome, D. Foliart, *Effects on Human Health of Pollutants in the South Coast Air Basin* (South Coast Air Quality Management District, El Monte, CA, 1989).
14. C. C. White, K. E. Powell, G. C. Hogelin, E. M. Gentry, M. R. Forman, *Am. J. Prev. Med.* **3**, 304 (1987).
15. E. T. Loehman *et al.*, *J. Environ. Manag. Econ.* **6**, 222 (1979).
16. M. Dickie *et al.*, *Improving Accuracy and Reducing Costs of Environmental Benefit Assessments* (U.S. Environmental Protection Agency Office of Policy Analysis, Washington, DC, 1987).
17. G. S. Tolley and L. Babcock, *Valuation of Reductions in Human Health Symptoms and Risks* (Final Report, U.S. Environmental Protection Agency Office of Policy Analysis, Washington, DC, 1986).
18. T. J. Kulle, L. R. Sauder, J. R. Hebel, M. D. Chatham, *Am. Rev. Respir. Dis.* **132**, 35 (1985).
19. W. F. McDonnell *et al.*, *J. Appl. Physiol. Respir. Environ. Exercise Physiol.* **54**, 1345 (1983).
20. M. Imai, K. Yoshida, D. J. Kotchmar, S. D. Lee, *J. Air Pollut. Control Assoc.* **35**, 103 (1985).
21. M. Kleinman, *J. Exposure Assess. Environ. Epidem.* **1**, 309 (1991).
22. D. I. Hammer, V. Hasselblad, B. Portney, P. F. Wehrle, *Arch. Environ. Health* **28**, 255 (1974).
23. The mixture of pollutants in Japanese cities is probably different from that currently found in the basin; however, the presumed dominant symptom-related agent in both mixtures is O_3 or an irritant oxidant compound for which O_3 is a useful surrogate.
24. K. Makino and I. Miyoguichi, *Nippon Koshu Isei Zasshi* **2**, 421 (1975).
25. M. Lippmann, *J. Air Pollut. Control Assoc.* **39**, 672 (1989); D. M. Spektor *et al.*, *Am. Rev. Respir. Dis.* **137**, 313 (1988).
26. L. B. Lave and E. P. Seskin, *Science* **169**, 723 (1970); H. Ozkaynak and G. Thurston, *Risk Anal.* **7**, 449 (1987); L. B. Lave and E. P. Seskin, *Air Pollution and Human Mortality* (Johns Hopkins Univ. Press, Baltimore, MD, 1977).
27. J. Schwartz and A. Marcus, *Am. J. Epidem.* **13**, 185 (1990).
28. J. S. Evans, T. Tosteson, P. L. Kinney, *Environ. Int.* **10**, 55 (1984).
29. F. Lurmann, personal communication (1989).
30. B. D. Ostro, *J. Environ. Econ. Manag.* **14**, 87 (1987); P. R. Portney and J. Mullahy, *J. Urban Econ.* **20**, 21 (1986).
31. B. D. Ostro, *J. Environ. Econ. Manag.* **14**, 87 (1987).
32. G. D. Thurston, I. Kazuhiko, M. Lippmann, C. Hayes, *Environ. Health Perspect.* **79**, 73 (1989).
33. *Accident Facts* (National Safety Council, Washington, DC, 1988).
34. Mid-values for cough, throat irritation, and headaches were derived from (*15*). Eye irritation estimates were averaged with those from (*35*). The mid-value for chest congestion was aggregated from values for cough and shortness of breath (*15*) because these symptoms partially capture congestion, which was not a defined symptom in that study. High values were estimated from (*15–17*). In the absence of low values in the literature, we constructed these by noting the ratio between mid-values and high values for each symptom and assuming that this ratio held between low values and mid-values. Our low values are comparable to the mean values in (*16*). Data on average wages for the region were used to value work loss–related RADs for groups in the work force and for nonworking adults aged 18 to 64 (we assumed that the opportunity cost of time is reflected in the wage rate). The time value of homemakers was valued at the wage rate for in-home service providers. MRAD values were used for all other groups. This is fully described in (*36*).
35. R. Rowe, L. Chestnut, B. Ostro, *Santa Clara County Air Pollution Benefit Analysis* (U.S. Environmental Protection Agency, Washington, DC, 1987).
36. J. V. Hall *et al.*, *Economic Assessment of the Health Benefits from Improvements in Air Quality in the South Coast Air Basin* (Final Report, South Coast Air Quality Management District, El Monte, CA, 1989).
37. V. Brajer, J. V. Hall, R. Rowe, *Contemp. Policy Issues* **9**, 81 (1991).
38. D. Gegax, *Perceived Risk and the Marginal Value of Safety* (Working Paper, U.S. Environmental Protection Agency, Washington, DC, 1985); M. W. Jones-Lee, M. Hammerton, P. R. Phillips, *Econ. J.* **95**, 49 (1985); J. P. Leigh and R. N. Folsom, *Q. Rev. Econ. Bus.* **24**, 56 (1984); M. J. Moore and W. K. Viscusi, *J. Policy Anal. Manag.* **7**, 476 (1988); S. Kahn, *IEEE Technol. Soc.* **5**, 24 (1986).
39. A. Fisher, L. Chestnut, D. Violette, *J. Policy Anal. Manag.* **8**, 88 (1989).
40. W. K. Viscusi, in *Benefits Assessment: State of the Art*, J. D. Bentkover, Ed. (Reidel,

Dordrecht, 1986), pp. 193–210.
41. J. E. Garen, *Rev. Econ. Stat.* 70, 9 (1988).
42. M. Denny and C. Pinto, in *Production Economics: A Dual Approach to Theory and Applications*, M. Fuss and D. McFadden, Eds. (North-Holland, New York, 1978), pp. 249–267.
43. We appreciate the contributions of our colleagues R. Rowe, L. Chestnut, D. Foliart, L. Coyner, and A. Horwatt; the comments of G. Cass, T. Crocker, A. Fisher, J. R. Holmes, M. Lebowitz, M. Lippmann, R. Neutra, B. Ostro, W. Ott, B. Phalen, B. Mautz, A. L. Wilson, R. Sawyer, and W. Carter; the technical assistance of M. Poe and D. Shearer; and the input of E. Calafato, C. Liu, A. Lloyd, L. Moore, P. Leyden, M. Saperstein, D. Shikiya, B. Wallerstein, H. Kim, T. Wang, G. Palmer, A. Sherwood, B. Sullivan, M. Pisano, D. Westerdahl, T. Phillips, and P. Jenkins. This work was supported by the South Coast Air Quality Management District and the National Science Foundation.

Research Article

A Yeast Chromosomal Origin of DNA Replication Defined by Multiple Functional Elements

YORK MARAHRENS AND BRUCE STILLMAN

Although it has been demonstrated that discrete origins of DNA replication exist in eukaryotic cellular chromosomes, the detailed organization of a eukaryotic cellular origin remains to be determined. Linker substitution mutations were constructed across the entire *Saccharomyces cerevisiae* chromosomal origin, *ARS1*. Functional studies of these mutants revealed one essential element (A), which includes a match to the ARS consensus sequence, and three additional elements (B1, B2, and B3), which collectively are also essential for origin function. These four elements arranged exactly as in *ARS1*, but surrounded by completely unrelated sequence, functioned as an efficient origin. Element B3 is the binding site for the transcription factor–origin binding protein ABF1. Other transcription factor binding sites substitute for the B3 element and a trans-acting transcriptional activation domain is required. The multipartite nature of a chromosomal replication origin and the role of transcriptional activators in its function present a striking similarity to the organization of eukaryotic promoters.

ALTHOUGH CELLULAR ORIGINS OF DNA REPLICATION ARE poorly understood in most eukaryotes, short chromosomal sequences have been cloned in the yeast *Saccharomyces cerevisiae* that enable plasmids to replicate along with the cellular chromosomes in the S phase of each cell cycle (*1*). Such autonomously replicating sequences (ARS's) have been shown by two-dimensional agarose gel electrophoresis techniques to be authentic origins of replication in plasmids and in cellular chromosomes (*2, 3*). Interestingly, only a subset of *S. cerevisiae* ARS's are active origins at their native chromosomal positions (*3*).

All ARS's of both classes contain a match to a degenerate "ARS consensus sequence," 5′-$^{T}_{A}$TTTA$^{T}_{C}$$^{A}_{G}TTT^{T}_{A}$-3′ that is essential for ARS function (*4–7*). The sequence requirements of this element have been thoroughly characterized, and any one of numerous single point mutations in this sequence eliminates ARS function (*6*). Although the conservation of this element suggests that it is recognized by a sequence-specific DNA binding protein, no protein has yet been shown to function at this sequence. A single strand DNA binding protein that binds the T-rich strand of this sequence has been identified and purified (*8*), but is not known whether this protein functions in DNA replication.

A sequence (or sequences) flanking the consensus match is also essential for origin function. Such sequences have been poorly defined because deletion mutagenesis has often produced conflicting results. For example, deletion mutagenesis of an ARS revealed a strong dependence on the nature of the adjacent sequence (*9*). One effect of adjacent sequences that has been demonstrated is the suppression of ARS function when nucleosomes intrude on the origin (*10*). Despite the poor sequence definition, there have been several proposals for a role of the essential flanking region. Deletions that reduce origin efficiency have variously been correlated with the disruption of a DNA bend, a DNA unwinding element, weak homology to the ARS consensus sequence, and a nuclear scaffold attachment site (*11–15*). The binding of the protein ABF1 has also been suggested to be important for ARS function. Although ABF1 only binds to a subset of origins, deletions and substitutions that disrupt these ABF1 binding sites reduce the maintenance of plasmids (*16–19*).

For our study of the structure of a yeast origin of DNA replication, *ARS1* was chosen because it is a proven chromosomal origin of replication and the chromatin structure of this origin has been studied in plasmids and in the chromosome (*20, 21*). A deletion analysis has shown that *ARS1* can be divided into three domains, A, B, and C (*5*). Domain A contains an essential match to the ARS consensus sequence and domain B is a broad region to the 3′ side of the T-rich strand of the consensus match. Domains A and B are adequate for efficient ARS activity and all other ARS sequences examined displayed the same A-B organization (*7*). Domain C, however, may be present only in *ARS1*, and its weak effect was detected only in the absence of domain B. We have now undertaken a systematic search for functional elements in a 193-bp *ARS1* segment containing domains A and B and a part of domain C that shows strong ARS activity (*5, 18*).

The authors are at the Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, and the Graduate Program in Molecular and Cellular Biology, State University of New York at Stony Brook, NY 11794.