cosmetic—changes of its former structures and goals, we expect the links with the scientific community of Serbia and Montenegro to be more intensive than they were before 1990," says Croatia's deputy science minister, Davor Butkovic. Georgi Efremov, president of the Macedonian Academy of Sciences, notes that although there is a "paper contract" for scientific collaboration between his academy and the Serbian Academy of Arts and Sciences, there are currently no research projects or exchange of people or lecturers. But, he says, "with democracy in Serbia, collaboration will be reestablished—this is the general feeling for scientists in Macedonia, and I'm sure for Serbian scientists as well." Croatian biomedical researcher Krešimir Pavelić, of the Ruđer Bošković Institute, thinks that scientists "should be the ones who take the first step towards the normalization of relations between Croatia and Yugoslavia."

There are promising signs that the next generation is ready to mend fences. Marko Popovic, a biology undergraduate at the University of Belgrade, was surprised at how warmly he was received when he attended a 2-week biophysics summer school in Rovinj, Croatia, last month. "When I arrived in Zagreb, I was scared, because a Serb tends to get defensive there," says Popovic. "But once you start discussing science, political problems go away." At least that's the hope for scientists trying to rebuild their war-torn countries. **–RICHARD STONE**

With reporting by Robert Koenig in Croatia and Slovenia and Gillian Sandford in Belgrade.

ENDOCRINE DISRUPTERS

Panel Cautiously Confirms Low-Dose Effects

Expert panel says estrogenic chemicals can cause biological effects at levels below those normally found safe, but the implications for human health are unclear

Of all the evidence suggesting that hormone-like chemicals in the environment might be bending the gender of wildlife and people, a lab study 3 years ago sparked the greatest alarm. It suggested that minuscule amounts of a chemical that everyone is exposed to—in baby bottles and Tupperware, for example—could alter the reproductive organs of a developing mouse. Virtually no one had reported effects from so-called endocrine disrupters at such low levels before. The results suggested that the Environmental Protection Agency's (EPA's) plans to begin screening chemicals for estrogenic activity might have to be revised to detect effects at lower levels. The agency's conundrum only deepened when other labs—funded mainly by industry—couldn't replicate the findings.

Faced with the dueling studies and aware of other new research that might resolve the question, EPA enlisted the help of an expert panel.* Earlier this month it met to conduct an extensive review of the data. Chaired by toxicologist George Lucier, who recently retired from the National Institute of Environmental Health Sciences (NIEHS), the 36-member panel concluded that doses of some endocrine disrupters far below those normally found to be safe can indeed cause biological effects in lab animals—a finding that runs counter to the conventional wisdom in toxicology. Panel members cautioned, however, that scientists still don't know what relevance the subtle developmental changes observed in animals might have for human health.

The work that triggered this inquiry was conducted by reproductive biologist Fred vom Saal's group at the University of Missouri, Columbia. Published in 1997, the team's two studies found that at levels below the normal testing threshold, the potent chemical diethylstilbestrol (DES) had peculiar effects on the male offspring of pregnant mice. At some very low doses, it enlarged a fetal mouse's prostate, but levels above this had the opposite effect. If low doses of other chemicals produced effects with this same humped curve, then tests conducted at higher doses might be missing biological effects, vom Saal suggested. But it was the second study that proved most explosive: It found that the plastics ingredient bisphenol A enlarged the prostate in mouse fetuses at the extremely low levels—parts per billion—to which people are typically exposed.

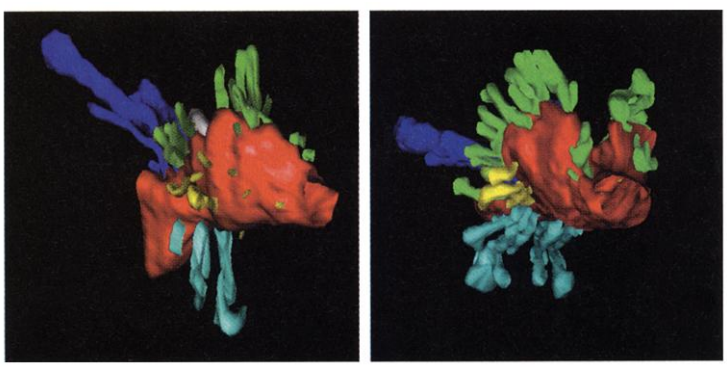
Alarmed about what the results might mean for the multibillion-dollar plastics industry, companies launched a wave of new research on bisphenol A. But attempts by John Ashby at the Zeneca Central Toxicology Laboratory in Cheshire, United Kingdom, among others, to replicate vom Saal's study with the same mouse strain, CF1, failed to find any bisphenol A or DES effects.

The task of sorting out these data fell to the expert panel, formed by NIEHS's National Toxicology Program at EPA's request. Its examination went "far, far beyond the usual peer review," notes Lucier. Authors of 38 studies submitted their raw data, including unpublished results, to the panel, which also heard presentations from key scientists.

The bisphenol A studies proved to be the biggest puzzle. The negative data included two major new studies by Japanese and industry-supported U.S. groups that found no effects of bisphenol A on developing rats or their offspring. But curiously, when the panel picked apart the protocols and data, a summary statement says it found that both vom Saal's studies and the negative ones were "credible and sound."

The discrepancies may be attributable to lab animals' exquisite sensitivity to estrogenic chemicals. As scientists noted, many factors—such as whether animals are fed or injected with chemicals, as well as their diet—can influence hormone levels. Another issue, reported in *Science* last year (20 August 1999, pp. 1190 and 1259), is that rodent strains can vary dramatically in their response to estrogenic compounds. Some scientists speculate that Ashby's CF1 mice might be genetically less sensitive to estrogens than the vom Saal mouse colony, which was maintained as an inbred group for many years.

Not all panelists were satisfied that the discrepancies have been explained, however. Vom Saal's results have "not been reproducibly established," insists biochemist George Stancel of the University of Texas, Houston, Health Sciences Center. Although a



Controversial result. Minuscule amounts of the common chemical bisphenol A fed to pregnant mice reportedly enlarged the prostate *(right)* in male fetuses.

CREDIT: B. TIMMS/UNIV. OF SOUTH DAKOTA AND F. VOM SAAL/UNIV. OF MISSOURI

* Endocrine Disruptors Low Dose Peer Review, Research Triangle Park, North Carolina, 10–12 October.

few other groups report that they've replicated the study, they either failed to submit their raw data or panelists found problems with the experiments. And vom Saal has destroyed his original strain of mice—so as to avoid mixing with a new type, he says—so nobody will ever be able to repeat his original bisphenol A experiment. Vom Saal's team reported at the meeting, however, that it has now gotten the same results with the new strain, CD1.

Other studies that showed an effect at low doses, though, were more straightforward, prompting the panel to conclude that low-dose effects from estrogenic compounds "have been clearly demonstrated." NIEHS researcher Retha Newbold, for example, has replicated vom Saal's inverted U curve for DES when looking at uterine changes in CD1 mice. And preliminary results from other federal studies have found alterations in brain and immune system development in rats from low doses of the plant estrogen genestein and nonylphenol, a chemical in detergents. How these results may relate to disease late in life in animals, let alone humans, is uncertain, say panel organizers. "It's not clear what the biological significance" may be, says pediatrician Lynn Goldman of Johns Hopkins University in Baltimore, Maryland, a former EPA official and a meeting organizer.

Pointing to these uncertainties, EPA's Anthony Maciorowski says it's "premature" to comment until the final report is out next spring. But he suggests that the agency may hold off on modifying its congressionally mandated screening program, which is set to begin testing commercial products in 2003. "If low-dose [effects] appear to play out, they can still be accommodated later," Maciorowski says. Lucier, for one, believes the evidence is strong enough: "I think there is reason for EPA to revisit" its testing requirements already, he says. But, he adds, the problem is not urgent. "If they're missing something [in the meantime], they're not missing anything catastrophic."

–JOCELYN KAISER

CLIMATOLOGY

Does a Climate Clock Get a Noisy Boost?

Ever-present climate noise may amplify a periodic nudging of the climate system, with dramatic past effects and uncertain future implications

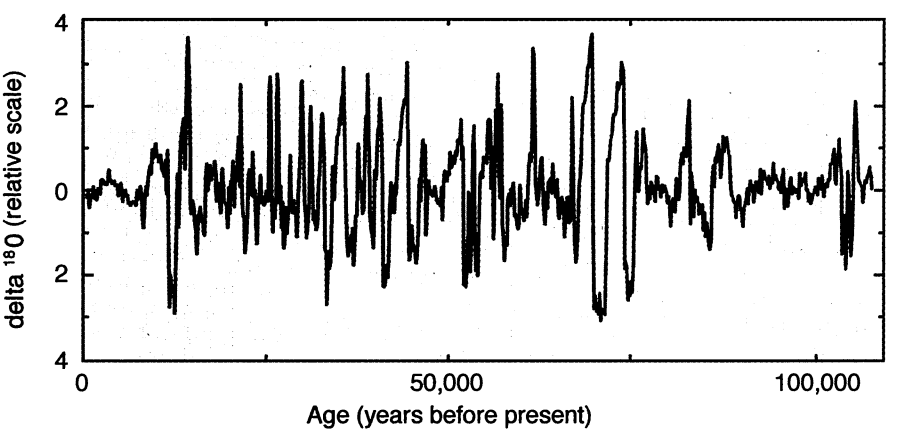
Noise has long exasperated researchers searching for signs of subtle regularity in geologic climate records. But noise may soon be viewed not just as an obstacle to understanding but also as an essential driver of climate change over the millennia. Three researchers pondering what could be behind a roughly 1500-year cycle of warming and cooling that most recently gave the world the Little Ice Age (*Science*, 25 June 1999, p. 2069) are suggesting that this millennial cycle is a combination of two climate drivers, each too weak to have a large effect on its own. When a strictly periodic cycle teams up with just the right amount of thoroughly irregular noise, the combination could achieve "stochastic resonance" and set off the dramatic climate shifts of the last ice age—or the next, possibly human-triggered, Little Ice Age.

In talks at recent gatherings, glaciologist Richard Alley of Pennsylvania State University, University Park; geophysicist Sidhar Anandakrishnan of the University of Alabama, Tuscaloosa; and physicist Peter Jung of Ohio University in Athens have presented an analysis of climate records preserved in Greenland ice cores that suggests stochastic resonance is behind the 1500-year climate cycle. If so, "noise also matters," says Alley. "What they describe is certainly consistent with stochastic resonance," says geophysicist Bruce Bills of Scripps Institution of Oceanography in La Jolla, California. "I came away feeling it was a quite plausible case." No one is claiming the case is proven, but if true it implies that "prediction is going to be really difficult," says Bills. That would complicate things as humans add in their own "climate noise" over coming centuries.

This isn't the first time researchers have invoked stochastic resonance to explain a climate cycle. In fact, the concept owes its origin to such a cycle. Now applied to everything from signal detection in electronic circuits to the neurophysiology of crayfish, stochastic resonance debuted in the early 1980s as a proposed explanation for the comings and goings of the ice ages every 100,000 years or so. If given a big enough push, the thinking went, Earth's climate system could flip between its two modes of operation, cold glacial periods and warm interglacial periods. But the only obvious means of setting the observed 100,000-year pacing—the rhythmic elongation of Earth's orbit—is too weak a driver to make the switch by itself.

Random—that is, stochastic—noise in the form of short-term climate fluctuations might help, the argument went, if it were strong enough. Increased just to the point at which noise plus the periodic signal suffice to switch the climate system from one mode to the next, noise would "resonate" with periodicity and an ice age would begin most but not every 100,000 years. Sometimes the system would skip a beat or two if by chance the noise were not strong enough when the periodic push was at its height.

Alley and his colleagues reunited stochastic resonance and climate after Alley happened to speak at Ohio University, where Jung applies stochastic resonance to neurophysiology. Alley was looking for drivers for the 1500-year cycle of moderate cooling and warming that punctuates the more dramatic 100,000-year ice age cycle. To test the 1500-year cycle for resonance, Alley, Anandakrishnan, and Jung gauged the durations of millennial climate cycles as recorded by the oxygen isotope composition of the 110,000-year Greenland Ice Core Project (GRIP) ice core from central Greenland. If the cycle were strictly peri-



SOURCE: ALLEY *ET AL.* AND GRIP

Ganging up on climate? A combination of weak climate noise and a weak periodic climate driver, such as a varying sun, may have combined to produce the climate spikes seen in this ice core record.