have not been verified as such. A
bioinformaticist’s “driver muta-
tion” is another’s “passenger
mutation.” Basket studies are a
good way of deriving preliminary
information on mutations that
are potentially responsive in hu-
mans to a specific drug — but to
design such studies for every po-
tential target mutation, for all
possible drugs, in all possible
anatomical sites, will be beyond
the capacity of our current inves-
tigator- and company-initiated
system of trials. Plans are under
way for larger phase 2 studies
such as the National Cancer Insti-
tute’s Molecular Analysis for Ther-
apy (NCI MATCH) II study, which
will enroll about 1000 patients in
about 20 mutation-specific groups,
but even a larger effort like that
one will capture only a small
fraction of the targeted therapies
being used off-label on the basis of
tumor-sequencing data.

Thus, the basket trials are a
useful first step in what should
be a multistep process. The next
step, where feasible, could be larg-
er anatomical-site–specific phase 3
trials comparing the drug–muta-
tion combination with the stan-
dard of care. In addition, given
the sample-size, logistic, and
financial constraints that make
phase 3 studies difficult for less-
common cancers and less-com-
mon mutations, establishment of
registries of off-label use would be
extremely helpful. Aggregated
observational data will always be
superior to “n of 1” anecdotes or
small series. Precedents exist, in-
cluding the “phase 4” postmarket-
surveillance studies that the
FDA has mandated in order to
gather evidence regarding both
possible differences in efficacy
for various subgroups and long-
term toxicity. Some cancer cen-
ters and professional societies
are collaborating to develop re-
gional databases. It is critical
that results from these databases
behave as transparent as those
from clinical trials — proprie-
tary databases will lead to com-
peting but unverifiable claims.
Developing such observational
databases is far from trivial, but
the costs per patient would be
small in relation to the monthly
costs of many of the targeted
therapies. Perhaps the plural of
anecdote could be data after all.

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GMOs, Herbicides, and Public Health
Philip J. Landrigan, M.D., and Charles Benbrook, Ph.D.

G enetically modified organ-
isms (GMOs) are not high
on most physicians’ worry lists.
If we think at all about biotech-
nology, most of us probably fo-
cus on direct threats to human
health, such as prospects for con-
verting pathogens to biologic
weapons or the implications of
new technologies for editing the
human germline. But while those
debates simmer, the application
of biotechnology to agriculture
has been rapid and aggressive.
The vast majority of the corn and
soybeans grown in the United
States are now genetically engi-
neered. Foods produced from
GM crops have become ubiqui-
tous. And unlike regulatory bod-
ies in 64 other countries, the
Food and Drug Administration
(FDA) does not require labeling
of GM foods.

Two recent developments are
dramatically changing the GMO
landscape. First, there have been
sharp increases in the amounts
and numbers of chemical herbi-
cides applied to GM crops, and
still further increases — the
largest in a generation — are
scheduled to occur in the next
few years. Second, the Interna-
tional Agency for Research on
Cancer (IARC) has classified
glyphosate, the herbicide most
widely used on GM crops, as a
“probable human carcinogen”
and classified a second herbicide,
2,4-dichlorophenoxyacetic acid
(2,4-D), as a “possible human
carcinogen.”

The application of genetic en-
gineering to agriculture builds
on the ancient practice of selective breeding. But unlike traditional selective breeding, genetic engineering vastly expands the range of traits that can be moved into plants and enables breeders to import DNA from virtually anywhere in the biosphere. Depending on the traits selected, genetically engineered crops can increase yields, thrive when irrigated with salty water, or produce fruits and vegetables resistant to mold and rot.

The National Academy of Sciences has twice reviewed the safety of GM crops — in 2000 and 2004. Those reviews, which focused almost entirely on the genetic aspects of biotechnology, concluded that GM crops pose no unique hazards to human health. They noted that genetic transformation has the potential to produce unanticipated allergens or toxins and might alter the nutritional quality of food. Both reports recommended development of new risk-assessment tools and postmarketing surveillance. Those recommendations have largely gone unheeded.

Herbicide resistance is the main characteristic that the biotechnology industry has chosen to introduce into plants. Corn and soybeans with genetically engineered tolerance to glyphosate (Roundup) were first introduced in the mid-1990s. These “Roundup Ready” crops now account for more than 90% of the corn and soybeans planted in the United States. Their advantage, especially in the first years after introduction, is that they greatly simplify weed management. Farmers can spray herbicide both before and during the growing season, leaving their crops unharmed.

But widespread adoption of herbicide-resistant crops has led to overreliance on herbicides and, in particular, on glyphosate. In the United States, glyphosate use has increased by a factor of more than 250 — from 0.4 million kg in 1974 to 113 million kg in 2014. Global use has increased by a factor of more than 10. Not surprisingly, glyphosate-resistant weeds have emerged and are found today on nearly 100 million acres in 36 states. Fields must be now be treated with multiple herbicides, including 2,4-D, a component of the Agent Orange defoliant used in the Vietnam War.

The first of the two developments that raise fresh concerns about the safety of GM crops is a 2014 decision by the Environmental Protection Agency (EPA) to approve Enlist Duo, a new combination herbicide comprising glyphosate plus 2,4-D. Enlist Duo was formulated to combat herbicide resistance. It will be marketed in tandem with newly approved seeds genetically engineered to resist glyphosate, 2,4-D, and multiple other herbicides. The EPA anticipates that a 3-to-7-fold increase in 2,4-D use will result.

In our view, the science and the risk assessment supporting the Enlist Duo decision are flawed. The science consisted solely of toxicologic studies commissioned by the herbicide manufacturers in the 1980s and 1990s and never published, not an uncommon practice in U.S. pesticide regulation. These studies predated current knowledge of low-dose, endocrine-mediated, and epigenetic effects and were not designed to detect them. The risk assessment gave little consideration to potential health effects in infants and children, thus contravening federal pesticide law. It failed to consider ecologic impact, such as effects on the monarch butterfly and other pollinators. It considered only pure glyphosate, despite studies showing that formulated glyphosate that contains surfactants and adjuvants is more toxic than the pure compound.

The second new development is the determination by the IARC in 2015 that glyphosate is a “probable human carcinogen” and 2,4-D a “possible human carcinogen.” These classifications were based on comprehensive assessments of the toxicologic and epidemiologic literature that linked both herbicides to dose-related increases in malignant tumors at multiple anatomical sites in animals and linked glyphosate to an increased incidence of non-Hodgkin’s lymphoma in humans.

These developments suggest that GM foods and the herbicides applied to them may pose hazards to human health that were not examined in previous assessments. We believe that the time has therefore come to thoroughly reconsider all aspects of the safety of plant biotechnology. The National Academy of Sciences has convened a new committee to reassess the social, economic, environmental, and human health effects of GM crops. This development is welcome, but the committee’s report is not expected until at least 2016.

In the meantime, we offer two recommendations. First, we believe the EPA should delay implementation of its decision to permit use of Enlist Duo. This decision was made in haste. It was based on poorly designed and outdated studies and on an incomplete assessment of human exposure and environmental effects. It would have benefited from deeper consideration of independently funded studies published in the peer-reviewed literature.
And it preceded the recent IARC determinations on glyphosate and 2,4-D. Second, the National Toxicology Program should urgently assess the toxicology of pure glyphosate, formulated glyphosate, and mixtures of glyphosate and other herbicides.

Finally, we believe the time has come to revisit the United States’ reluctance to label GM foods. Labeling will deliver multiple benefits. It is essential for tracking emergence of novel food allergies and assessing effects of chemical herbicides applied to GM crops. It would respect the wishes of a growing number of consumers who insist they have a right to know what foods they are buying and how they were produced. And the argument that there is nothing new about genetic rearrangement misses the point that GM crops are now the agricultural products most heavily treated with herbicides and that two of these herbicides may pose risks of cancer. We hope, in light of this new information, that the FDA will reconsider labeling of GM foods and couple it with adequately funded, long-term postmarketing surveillance.

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