Episode Title: TSCA New Approach Methodologies -- A Conversation with James W. Cox

Episode Number: 20220915
Publication Date: September 15, 2022

All Things Chemical® is a podcast produced by Bergeson & Campbell, P.C. (B&C®), a Washington, D.C., law firm focusing on chemical law, business, and litigation matters.

This podcast transcript has been lightly edited for accuracy. It is an approximation of the podcast audio, and the audio recording remains the definitive record.

Let us know about any topics you would like to hear about in future episodes at podcast@lawbc.com.

A full recording of the podcast is available at https://www.lawbc.com/podcasts/tsca-new-approach-methodologies-a-conversation-with-james-w.-cox.

Lynn L. Bergeson (LLB): Hello, and welcome to All Things Chemical, a podcast produced by B&C, a Washington, D.C., law firm focusing on chemical law, business, and litigation matters. I'm Lynn Bergeson.

This week, I had the pleasure of sitting down with James Cox, a Senior Scientist with B&C. James is an exceptional biologist with significant experience assessing the risk of industrial chemicals. Before joining B&C earlier this year, James served in a variety of leadership positions in the U.S. Environmental Protection Agency's (EPA) Office of Pollution Prevention and Toxics (OPPT). One such position was Chair of the Risk Assessment Technical Team, which provides recommendations to inform EPA's policy positions on new approach methodologies, otherwise known as NAMs, a subject we're hearing an awful lot about in connection with [the Toxic Substances Control Act] TSCA, I discuss with James NAMs, their significance in TSCA risk assessments, how NAMs will enable diminished reliance on animal testing, and some of the challenges facing chemical stakeholders in moving away from animal testing. Now here is my conversation with James Cox.

James, I am so excited about our conversation. Thank you for joining me today.

James W. Cox (JWC): Thank you for inviting me.

LLB: You are most welcome. Listen, you've been with the B&C team now a number of months. I'm just thrilled that you are part of our team. I would welcome an opportunity for you to share a little bit about your background with our listeners. You were with EPA a number of years. What did you do there?

JWC: Yes, I was with EPA for I guess not quite four years, where I worked in what used to be the Risk Assessment Division in OPPT, and I concentrated mostly on human health risk assessments for new chemicals. And in the fall of about 2020, I think, the reorganization occurred, and the New Chemicals Division (NCD) was born. And I was reassigned to NCD,

where I continued to do much of the same work, assessing new chemicals from a human health perspective and various other side projects as well.

LLB: Well, EPA's loss is definitely our gain, James, and we very much have welcomed the opportunity to work with you. That brings us to our conversation today. There has been just a great deal of talk lately about new approach methodologies otherwise known as NAMS. They've been described, kind of generally, as any technology, methodology, approach, or combination thereof, used to assess a chemical's hazard and assist with its risk assessment without the use of animals.

I understand that NAMs are not necessarily *new* methodologies, but rather what makes them new is their utility in risk regulatory decision making as a replacement to traditional animal testing. So a couple of questions. Number one, is this correct? And is it also correct to note that NAMs are, in addition to diminishing our reliance upon animal testing, also intended to speed and diminish the cost of screening chemicals in identifying adverse biological effects? I know that's a long question, James, but why don't you take a shot at it?

JWC: Sure. I think that both pieces of your question are pretty spot on. It is not necessarily the case that the technologies or the methodologies themselves are new or novel *per se*, but rather the application of the technologies and their acceptance into the regulatory ecosystem that is new. In some cases, we might be talking about well-established technologies that are perhaps decades old, and yet there's been a delay between the development of the methodology, which has accelerated greatly -- probably within the past decade or so -- and the validation, the acceptance, the implementation of the methodology into the regulatory environment.

Some of the factors that one might point to in an effort to explain this delay are sometimes the purpose of the NAM is not clearly defined. For example, what we mean is what is it that we're seeking to replace with this new methodology? And there's also the fact that in laboratory ring trials -- and these are used to establish the reproducibility, the repeatability, etc. -- both of animal methods and of NAMs, which are key components for validation and acceptance of the NAMs. These are expensive. These are lengthy. These require coordination among various stakeholders and various laboratories.

And perhaps most importantly, the international regulatory agencies have used predictive capacity as an indicator whether a NAM should be considered to be relevant and acceptable. But that predictive capacity -- when I say predictive capacity, I mean the ability to predict the desired effect in humans, and so therefore be protective of that. As it turns out, that's sometimes been based on comparisons to animal test methods for which the reproducibility and the biological relevance were assumed rather than empirically demonstrated. And as it turns out, sometimes it's not necessarily the case that the animal method *was* as predictive as it was assumed to be.

I think for the second piece of your question, I think that you're also right. I think that we would like to refine, reduce, and replace the use of animals for research purposes, but it's also potentially a way to get data faster, get data more cheaply. And these are all things that, I can tell you in my time in the regulatory environment, would be a welcome change and are necessary.

LLB: Absolutely. James, you just mentioned something that I did not know a moment ago, and that is that in the context of validating some of these NAMs and looking back over the predictive capacity of more traditional testing, it has been discovered that that predictive

capacity may not be quite as accurate as had previously been thought. Was that a surprising discovery, or do scientists more or less assume that you're always going to be learning things when you go back and reassess things along those lines?

JWC: So that's a good question. With most issues, I'm certain that if you interviewed ten scientists, you might get ten different nuances on the answer. I think that we should always have an open mind and be willing to accept the changes that may come about through new investigations. And yet, I think it *was* surprising, and it was surprising for myself. When I was doing research earlier in my career, I spent a large amount of my time doing animal research. And I sort of had a tendency to hang my hat on that as sort of the gold standard of data.

LLB: Yes, you're not alone there, right?

JWC: Yes. And you have to examine, is this me being biased, or is this simply -- or am I hanging onto this for a good reason? So introspection is good.

LLB: Yes. I know when I was preparing for this podcast, I was poking around trying to get some really good definitions of NAMs because it's a term that is tossed about a lot in TSCA circles. And I know our listeners are very sophisticated industrial chemical aficionados, but there are a couple of terms that might be helpful to just put on the table here.

Another definition of NAM is commonly defined to include *in silico* approaches, *in chemico* approaches, and *in vitro* assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard assessment. So those *in chemico, in vitro*, and *in silico* -- can you maybe just walk us through what those terms might refer to in the context of defining NAMs?

JWC: Sure. Yes, no problem. As you touched on, NAMs are viewed as a new technology, methodology, or approach, or some combination thereof that seeks to refine, reduce, or replace the use of animals in toxicity testing. And it has been tempting for me, I'm sure for others as well, it's tempting to think of this as a simple paradigm shift from *in vivo* or live animal testing to *in vitro* testing, which uses human or animal cells to investigate a particular issue. But in reality, it's much more nuanced than that. As you touched on, when we talk about NAMs, we mean a variety of things, ranging from the *in vitro* assays using the cells that I just spoke about to *in chemico* assays.

What *in chemico* assays do is they evaluate the chemical interactions or reactions with certain materials. A great example of this would be for the recent OECD [Organization for Economic Cooperation and Development] guideline for skin sensitization. One of the first -- the first assay used would be the DPRA, the direct peptide [reactivity] assay, which basically is an *in chemico* assay that seeks to find out does the chemical in question interact with and therefore deplete concentrations of amino acids found in human proteins, like lysine 16.

So that's an example of *in chemico*; and *in silico* tools are computer-driven predictive tools. We use the *in silico* tool -- I say we; I should say EPA uses *in silico* tools -- and other regulatory bodies -- that extend beyond mere hazard identification. For example, you might see the use of *in silico* tools or predictive models to aid in exposure prediction. And EPA has a list of accepted NAMs in accordance with TSCA, and they update those as necessary. And some of them, some examples are as follows. For example, in March of 2021, EPA announced an external peer review document for its multipath particle dosimetry or MPPD

[multiple-path particle dosimetry model] software, which aids in the assessment of inhaled materials.

LLB: Yes.

JWC: I think the software was based on principles of original deposit dose ratio modeling established back in 1994. And it was fit to a unique set of experimental data from inhalation studies across five laboratory animal species and commonly used in testing for regulatory risk assessment, as well as for humans. The model provides predictive power for inhaled deposited doses in various regions of the respiratory tract, including extrathoracic, tracheobronchial, and pulmonary or total respiratory tract. And so as mechanistic modeling technology has improved since 1994, we've arrived at a place where the MPPD can provide us with potentially much more robust and nuanced information about inhalation risk than you might see from a 90-day inhalation toxicity study in rats, where what you walk away with is a point of departure. And so potentially the MPPD software can give you much more nuanced information than that.

LLB: No, that's huge. Is that to say that if a chemical stakeholder were to receive some sort of test order or otherwise wish to produce a 90-day inhalation study on rats, you could instead use this MPPD software as a substitute and perhaps avoid that kind of animal testing?

JWC: Potentially. That would be the real prize, wouldn't it?

LLB: Well, certainly for the rats. Yes.

JWC: For sure. Another example I can think of is EPA's use of a species sensitivity distribution (SSD) toolbox on their final risk assessment for trichloroethylene in November 2020. And essentially, what SSD -- typically, my experience is in human health risk assessment. And that's kind of where my mind sits most of the time. But there's a world beyond that. And essentially SSD is a type of probability distribution of toxicity values for multiple species, such as fish and amphibians and invertebrates. And it can be used not only to visualize which species are going to be the most sensitive to toxic chemical exposure, but [it] can also predict the concentration that would be hazardous to a percentage of test species. If we set that percentage sufficiently low enough, we could use, for example, a hazardous concentration threshold of 5% of species, which means that that concentration, while harmful to 5% of species, is protective of 95% of the species.

LLB: Yes.

JWC: That's a split that we commonly -- or we like to -- see in science. But in the last example, probably the dearest to me is, you know -- and I touched on this a bit earlier -- is EPA's contribution to what eventually became the OECD Test Guideline 497, which was the Defined Approaches on Skin Sensitization. And it is a combination, as I said, a combination of *in chemico* and *in vitro* tests, that taken together can give us information about a molecular initiating event, which would be the interaction with the amino acids that I spoke about and a couple of key intermediate events. The termination of these events would be the adverse effect that we're trying to be protective of, which would be the allergic contact dermatitis. It's been great success with that. The predictive power is well established. And I think that we hit a homerun with that one.

LLB: NAMs as a concept and the terminology itself have been around for a while -- right? -- I know at least since 2007, and probably even before that. Is a lot of the focus on NAMs now

derivative of the 2016 enactment of [the Frank R. Lautenberg Chemical Safety for the 21st Century Act] (Lautenberg) that really telegraphed Congress's desire that EPA transition away from animal testing and pursue alternatives to that? Or is there another driver here?

JWC: This will probably be somewhat of an anecdotal response, so try to keep that in mind.

LLB: That's okay.

JWC: But I think that you're partially correct -- that the current awareness and push for NAMs is a derivative of Lautenberg -- but I think there are many factors in play. As a result of that change in the law, Administrator Wheeler definitely made it a policy priority for validation acceptance of NAMs. And I think that's probably carried on through the current Administration.

LLB: For the benefit of our listeners, as we all know, Andrew Wheeler was Administrator of EPA during the Trump Administration. And I know that in September 2019, he issued a memorandum or a dictate of some sort that really solidified and crystallized EPA's commitment to diminish and reduce, if not try to eliminate, animal testing by, I think 2025. I may be wrong on that, but certainly try to do a significant amount, a big reduction, by 2025 and then ultimately ease off of animal testing generally. So I just wanted to throw that in there because I know Andy Wheeler was very committed to diminished animal testing. And that commitment, I'm sure, has been embraced, if not reinforced by the current Administration, correct?

JWC: Yes, I'd say that's accurate. Additionally, I think along with that, there's definitely the push for NAMs. We're seeing the trickle-down effect from -- there's an impact of external stakeholders as well, such as the Physicians Committee for Responsible Medicine (PCRM) or the PETA [People for the Ethical Treatment of Animals] Science Consortium International (PSCI). They've been talking about this for a long time, and they've been very vocal. And I think that the regulatory community is listening and starting to take notice. We sort of touched on one earlier. One of your questions asked about is this also potentially a benefit -- would be not only to reduce and perhaps eventually replace animal testing altogether, but come up with a more economical and speedy way to get data to the regulators. I can tell you that in my time in OPPT, that was -- if we could get more data more quickly, that would have been a game changer for us.

LLB: Yes. With some 40,000 existing active chemicals, we need all the help we can get, right? Because there are lots and lots and lots of data gaps out there. And so NAMS are intended also to speed the ability to plug those gaps and conduct really good risk evaluations.

JWC: Yes, exactly.

LLB: I appreciate that chemical testing is hugely important to government agencies, including EPA, of course, which EPA is tasked with assuring chemical safety. This kind of circles back to that all-important question of who decides whether a NAM is a suitable substitute for animal testing, especially when, for years and years and years globally, we have been relying upon testing guidelines that are well understood and validated. We're all familiar with the OECD test guidelines, for example. Tell us a little bit about that process so that we can understand how we should have confidence in NAMS going forward.

JWC: Right. Sure. A couple of layers to my response here. You're right. As you pointed out at the end of your question, OECD published the guidelines for the assessment of chemical effects

on human health and the environment. There's a Mutual Acceptance of Data (MAD) agreement among the 38 member countries of OECD, which aimed to reduce duplicate testing, and data generated in the testing of the chemicals in an OECD member country in accordance with test guidelines and Good Laboratory [Practice] (GLP) principles should be accepted in other member countries.

There is some discretion, however. Regulatory agencies can decide which OECD test guidelines to require, and they can decide themselves whether or not to accept non-guideline methods that perhaps haven't been accepted by OECD yet. The 2009 International Cooperation on Alternative Test Methods, or ICATM, was originally established in the U.S.-International -- excuse me -- by the U.S. Interagency Coordinating Committee for Validation of Alternative Methods, which we more commonly call ICCVAM, Health Canada, and the European Union (EU).

In the case of chemical testing particularly, I can speak to not just regulations under TSCA, but probably [the Federal Insecticide, Fungicide, and Rodenticide Act] FIFRA, too, so we're talking about [EPA's Office of Pesticide Programs] OPP and OPPT. Health Canada and ECHA [the European Chemicals Agency], they enjoy some discretion as to the acceptance of the NAMs, which I think is predicated heavily upon the regulatory flexibility which govern them to accept those NAMs. And I can tell you that that flexibility does exist under TSCA. I'm pretty sure it exists under FIFRA as well. So these would be all the factors in play as to whether or not to accept a NAM. And, of course, as we spoke about earlier, we need to gather the data, and we need to -- there's a whole -- when you gather data and you show things like reproducibility and repeatability, you have to have it reviewed and validated, and so forth. So it's a large cooperative effort of multiple stakeholders.

LLB: That helps because it sounds like to us non-scientists -- as a lawyer and as someone who is often trying to advocate on behalf of my clients, the firm's clients, we are always trying to put our best foot forward with respect to the suitability of an alternative approach to something which EPA or other authoritative body may be asking of us. It's comforting to know that there are international treaties, ICCVAM, [the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods] NICEATM, and other standards that provide a general working framework for the acceptability of these alternatives to more traditional animal testing, which have been around for so long and are so highly regarded. And I might be misstating things here, James, but animal testing seems to be still kind of the gold standard, right? Or maybe that's a misstatement. Are NAMs now becoming the gold standard?

JWC: Yes, okay. Great question. I think that most regulatory scientists would probably agree that the gold standard is probably still viewed as animal data. There's more and more -- and there are multiple reasons for that -- and as I said, I know that within my own mind, it's what I've -- when I think of how to design an experiment, I normally think of how many animals do I need? How many test groups do I need, that sort of thing. What will give me statistical significance?

LLB: Right.

JWC: That sort of thing. And that's not necessarily -- so being aware of that, I have to examine, is this my own bias? Is this my own experience talking? So we have to be aware of that as well. But I think that alternative methods definitely are gaining more acceptance and reliability. And as we talked [about] earlier, there is starting to be evidence to show that

perhaps the reliance upon the animal study as the standard of translatability to human health is not necessarily always -- it's sometimes a bad assumption; it's not necessarily the case.

LLB: Yes, no. That was a very interesting observation you offered. And I simply did not appreciate that. But of course, you're right. That's now kind of -- of course, those observations might be elicited as a consequence of going back and truth-testing the reliability.

JWC: And we shouldn't be surprised.

LLB: We shouldn't be surprised, right. Right. I'm surprised, but EPA scientists are not.

JWC: But I think -- you asked about -- I just wanted to comment anecdotally that I can tell you from my own experience that when -- if something, whether it be a study or a method or whatever, if something has been accepted by and used by another regulatory agency, to me in my -- and then put into practice for things like risk assessment, to me that gives it some weight. And I think that is sort of the spirit behind the MAD agreement, for example, that OECD has. And I do -- I think that a lot of people would probably agree with that as well, that "Hey, look, Health Canada is doing this, and it's working for them. Shouldn't that mean something?"

LLB: Oh, I completely agree. And I -- maybe I'm going out on a limb here, too, James. But to the extent the EU has disavowed animal testing, I think for a longer period of time, and I don't mean to say disavow, but certainly has demonstrated a desire to transition to non-testing -- animal testing -- alternatives earlier than in the United States. Given our ability to mutually rely upon validated data in the EU under REACH [the Registration, Evaluation, Authorization and Restriction of Chemicals], for example, for purposes of providing information to EPA, for TSCA purposes, those types of mutuality agreements and the interchangeability of scientific standards in chemical testing are absolutely essential. So it's comforting to know that in Canada, the European Union, and in other authoritative bodies with which we deal and rely upon for purposes of the reliability of data generated in those countries under those frameworks, that you have a high confidence level that these things are proceeding in a way that should give everyone comfort that NAMs are progressing and can be relied upon for purposes of chemical risk evaluation.

JWC: That's right.

LLB: All right. Let me ask you a question that -- I was pondering this in preparing for this conversation. Are there instances, to your knowledge, James, where there's simply no substitute for an animal test, and a NAM may not work? Is there a finite -- or infinite -- number of instances where that may be a true statement?

JWC: Great question. Not an easy one to answer. I think it depends very heavily upon how well we understand the mode of action -- or perhaps more correctly -- the adverse outcome pathway.

LLB: Yes.

JWC: If we have a good handle, the scientific underpinnings of that adverse outcome pathway, then we can seek to investigate things like the key events in a sensitization pathway that the testing guideline was based upon and develop a weight of evidence approach for that. I can think, for example, an area where this might be tricky would be in the area of reproductive

and developmental toxicity because that's an endpoint that can have multiple different mechanisms that all would perhaps lead to reclassification of -- the identification of the endpoint itself. So that's an area that perhaps might be tricky. But as I said, I think the entirety of it is probably how well we understand the underpinnings of the adverse outcome pathway itself.

LLB: Your response invites a kind of a parallel, or companion, question: to the extent that the goal here of NAMs is to certainly diminish, if not eliminate, animal testing, would everyone in the chemical stakeholder community necessarily agree that that's an objective in and of itself, maybe the diminished part, but not the eliminate part, especially when reasonable scientific minds might differ as to whether a reliable non-animal testing new approach methodology is a suitable alternative to animal testing?

JWC: Right.

LLB: Is there a vigorous disagreement in the community out there?

JWC: In my experience, there is vigorous disagreement about a great many things.

LLB: Well, true that. We needn't stick just to animal testing.

JWC: That's right. So the short answer would be, yes, I think that nobody would disagree that we'd like to have more data, particularly nobody from the world in which I existed prior to coming to B&C. I don't believe any of those folks would disagree that more data would be better. But certainly I couldn't -- I have had disagreements about which is better, animal or NAM data. And I've found myself, at differing times, on either side of the issue, to be honest.

It's a big issue, and it's a multi-layered, multi-faceted issue. And I don't -- I think that one of the better things that can happen would be international acceptance. It does seem that the EU tends to be a few years ahead of the United States in a lot of ways, and so I think that success elsewhere begets acceptance here. But I don't -- there will always be people who are doubtful about can -- this is perhaps a glib way of summarizing the controversy -- but can a plate of cells really give me as much information as a living, breathing biological system? And I think that that's the hurdle that we have to overcome.

LLB: Well, exactly. And like any other complex, extremely relevant scientific question, of course, you're going to have multiple views on the subject, right? But it's a big tent, and discussion and exchange and dialog are important. And in that regard -- and last question, James, can you give us any examples of successful collaborations between EPA and external partners, maybe, you know, the industrial chemical community, PCRM, PETA, you name it, who -- lots of stakeholders out there?

JWC: Sure, I can think of a handful of examples. EPA partnered with PSCI and others to coordinate a special issue devoted to NAMs in the journal *Frontiers in Toxicology -- In Vitro Toxicology*. And they also --

LLB: Was that recently? This year, last year?

JWC: Yes, the date escapes me -- might have been 2021, 2020, perhaps. I'm not sure.

And EPA's OPPT partnered with PSCI, Health Canada, and EPA's OPP, and various industry experts to publish an article on using NAMs to meet regulatory requirements for industrial chemicals and pesticides. That was also in *Frontiers in Toxicology*. Again, the date escapes me. And I can also think of EPA did partner with both PSCI and PCRM to host a series of public webinars promoting NAMs. They have advanced the science of NAMs through a series of presentations at Society of Toxicology annual meetings covering topics like lung effect categories for surfactants or poorly soluble, low-toxicity polymers and respiratory sensitization of isocyanide-based prepolymers. So those are a few examples where --

LLB: Those are great.

JWC: Yes.

LLB: Well, your experience and depth in this area, James, are obvious. Your former position as Chair of the Risk Assessment Technical Team at EPA advising EPA on NAMs is well recognized. Your depth in this area is invaluable to the firm, and I would hope our listeners would reach out to you to the extent that they have questions about NAMs, their suitability to replace animal testing, where this extremely important area is heading, and any other questions they may have. And I want to thank you, James, for sharing your expertise today and your passion for this space, because it's really evident.

JWC: You're most welcome. And thank you for the opportunity to speak on this.

LLB: You bet. We'll have you back soon. Thank you, James.

JWC: Thank you.

LLB: My thanks again to James Cox for speaking with me today about NAMs and how the industrial chemical community is settling into a world of chemical testing and risk assessment without the help of animals.

All Things Chemical is produced by Jackson Bierfeldt of Bierfeldt Audio LLC.