ILSI 2021 Annual Symposium Session 5: Considerations for Implementing Globally Harmonized Nutrient Reference Values

Sponsored by the American Society for Nutrition (ASN)

Transcript of the presentation, The Current Status of Developing Harmonized NRVs, Lindsay Allen, PhD, USDA ARS Western Human Nutrition Research Center, University of California, Davis, United Sates

Yeah, very, very happy to be with this group of people who are really thinking about harmonization of nutrient reference values. And what I hope to do is follow up and expand on what's been happening since last year in Costa Rica, where we were very happily at our meeting and discussing all this together. But I hope that sort of update you a little on what has been happening.

So, next slide are my disclosures. My disclosures are that I'm funded by the Bill & Melinda Gates Foundation, Wellcome Trust, I'm president of ASN, and I'm on number of science scientific advisory committees and unpaid positions. There's no conflict of interest. Next slide.

So, what I'm trying to do today is do a brief summary to start with on which values are needed. The terms "dietary reference intakes" and "nutrient reference values" mean the same thing in my presentation, we've evolved from DRIs in some countries to NRVs, is it's a more international concept. So, I'm going to talk about why we need two particular values that many people do not have at this point in time. Talk about the National Academy's process to harmonize the approach to setting NRVs. That can be confusing, and I hope that we can differentiate between harmonizing the approach, the way that you set NRVs, and down here, later, the actual harmonized values that I have proposed along with some colleagues. So, we're going to talk about the process of harmonizing, the approach, the toolkit that Connie mentioned that came out this past year, harmonized values, and the big discussion I would like to have is, can we use globally harmonized values for NRVs, which is what Connie was suggesting might be possible. And then a little bit about future plans. Next slide.

So, this is the terminology for nutrient reference values. The two yellow are the most important nutrient reference values. The average requirement, which is the average requirement of a population group, and the upper nutrient level, which is the intake level, which says increased risk of adverse effects of intakes at that level. In between, there's something called the individual nutrient level, the RDA, RNI, PRI, depending on which group is setting that. And that is for individuals, not for population application. And it's usually about two standard deviations above the average nutrient requirement, or the average requirement. Next slide.

So, which NRV to use for which purpose? The EAR, again, is very prominent here for assessing adequacy of intake of individuals, you use the EAR, and of populations, you use the EAR. For planning diets for individuals, you use the RDA, but for population groups, you need to arrange an intake level, which is

between the EAR [inaudible 00:30:14] is called the target median intake. And this is, I would say a concept which has been expanded by this paper in March of this year, by Suzanne Murphy, and the [inaudible 00:30:29] for the National Academy, and Alicia Carriquiry. And this talks about how you use the NRV values for a childcare and adult care food program, for planning the program. So that's how you plan for your population group. So, why are we really anxious about these nutrient reference values out there? Where they have many, many uses listed in the first bullet, planning, food-based dietary guidelines, food programs.

I really first got into this, or lots of it, for planning food fortification. You need the same values across countries, really, when you're doing that, and you need EARs and ULs. For many, many purposes, then, we need NRVs, but there are lacking ARS and ULs in many countries and agencies. I know some in Southeast Asia, I think, are lacking those ARS in particular, and FAO WHO has almost none of those either. So instead, people are using RDAs or RNIs, which are supposed to meet the requirements of almost everybody in a sex age group.

And so, if you're evaluating prevalence of inadequate intakes against the RDAs, you are vastly overestimating the prevalence of nutrient inadequacy, or inadequate nutrient intakes. So, to my mind, having ARs and ULs to assess intake, adequacy, and safety is much more important than huge efforts, as some countries or regions go to every five or 10 years, and fine tuning the RDAs. The RDAs are not that useful.

Finally, I don't think we're going to suddenly get more scientific investment in filling in these gaps. The gaps are there because they're often caused by having a difficult population group, perinatal period, young children, and so on. And the cost of redoing systematic reviews is very prohibitive. Next slide.

So, the National Academy has been one of the leaders in talking about the need to use the same approach to deriving NRVs, not necessarily the same values, but the same approach. And this would vastly help the transparency of the values and enable nutrient review panels to use each other's information. It would provide support for LMICS, low middle income countries to adapt the existing DRIs to their population, comparing intake adequacy across populations. And then this would be a common basis for establishing nutrient policies, such as fortification, feeding programs, regulation, and trade. And Anna today is going to talk about the latter of those. So, this is the approach, and this is the book that came out in 2019.

And this is the book that came out in 2019 available on the web on the approach, the generic method for developing NRVs. So, the focus is on setting an AR and the UL and improving access to tools and data for setting intake recommendations. Then this was followed by a tool kit that we'll also talk about, it's also in this book talking about the generic resources that are needed to do this job, the huge resources needed to do this job and how can we share them better? How can we make them available in data banks? And it lays out essentially the choice of setting, how people set recommendations. You could derive a whole new set of NRVs or modify some existing NRVs that are available currently locally or globally, or just use existing NRVs since you've been published that just spending tens of millions of dollars by the IOM, Institute of Medicine, and the European Food Safety Authority, for example.

And then finally, I'm going to suggest that we have, in fact harmonized, the EFSA and National Academy NRVs, and perhaps those would be useful. Okay, next slide. So, this not very clear picture is from the tool kit from The National Academy published last year. And it essentially lays out that two-pronged approach, which I was mentioning, whatever you do at the beginning, you have to get expert panels,

evaluate the existing values, and we'll hear from Anura what they did in India, along these lines. I'm very interested to hear his presentation on this. And so, on the left-hand side, it's not establishing completely new ones, keep the old ones, update, adapt them, but you still have to describe all the outcomes you selected, the approach you use, get the evidence base, evaluate usual intakes and dietary patterns of your population. And that's simply to really getting dietary information it's useful for bioavailability estimates, for setting the values for the absorbed nutrients, and then finally decide whether to adjust your own values and how to do that.

The right-hand side is if you want to start from scratch, establishing new NRVs and the methods you use, it could be dose-response assessment, factorial approach, and you go through again, looking at dietary patterns to get bioavailability, assess the local context and decide whether to accept revise or derive NRVs. So, this tool kit has a start on supplying information, which should be useful for everybody. Now, where can you get the resources and dietary intake? If you haven't done it in your particular country, what are some of the bioavailability adjustments and so on? It's not finished yet. The National Academy wishes to proceed with this in the next few years. Next slide.

This is a slide that actually Ken Brown out together for another meeting we had recently and just shows the steps that FAO, WHO, EFSA and the national academies go through to develop their dietary reference values or their NRVs. I should have called those. He called them DRVs. And so, for example, here's the FAO process and they're starting right now to revise the recommendations for young children. So, they have a [inaudible 00:38:23] group, a scoping review The National Academy does that too. Is there enough new literature to make a different? Should we do this? You've got to have the problem formation particular format called PECO to do that in a public consultation The National Academy, moving over to the right, does this systematic review. Systematic reviews are hugely expensive and there should be a repository for these.

So systematic reviews, expert reviews, consultations on and on. At the bottom here, it takes 12 to 36 months for FAO, WHO, to come up with a value for a nutrient or maybe a couple of nutrients. And it costs 10 to a $100,000 per review and a lot of stuff and volunteer time. The National Academy estimates $1 million per nutrient and 18 months to go through this process. They're doing it, I believe, for riboflavin, for example, right now. So huge expense, huge amount of time. And so, we have to keep in mind, is it worth it in the end? And I think Anura's presentation will maybe shed some light on that. Next slide.

So why develop these harmonized values? In fact, it's very unlikely that requirements for absorbed nutrients differ much across populations. They use for setting diets, dietary recommendations and guidelines is what differs. And obviously that's different for each country depending on their food supply. There are all these missing values that we need, we don't have. IOM and EFSA values infants and children, and to be extrapolated anyway, from the infant, adequate intake or the additive adult values. So, there's some very implausible jumps in the NRVs. For example, calcium jumps doubles within a one-day period for young children. And we're kidding ourselves when we think these have to be accurate to a decimal point.

The true requirements are very variable among people. Estimates of bioavailability are very variable and intakes are uncertain. Cost and time needed to do this as prohibitive programs and evaluations are ongoing, and these values are needed. Next slide.

So, well. We did as a team, myself, Alicia Carriquiry and Suzanne Murphy, is we actually proposed harmonized values because we knew that the IOM and EFSA had done so much work on this. We took a look at what is missing when you combine these data sets and came up with good guesses, I think, for what the missing values should be. So, the purpose of them was to get as many AR and UL values as possible for global use out of these two reports and also applying around scientific judgment and the literature. Next slide.

So, what we're doing now, looking back at our graph here, is we're proposing on the left-hand side, harmonized average requirements and harmonized upper levels. And so, the EAR is now would be called the H-AR harmonized, and the upper level would be called harmonized upper level. Next slide. So, we used EFSA for most of this because these values were set most recently the IOM are now 20 or so years old, except for calcium and vitamin D. Also, EFSA did some systematic reviews on some nutrients. This systematic use of systematic reviews is relatively recent, and the IOM didn't use it when setting their values in the past only vitamin D and calcium, which in more recent reports. But there's still a lot of interest of missing information. EFSA only has ARs for seven vitamins and three minerals. IOM has it for 10 vitamins and nine minerals. So, we use the IOM if there was no EFSA value. And there were a few nutrients that we did that for, if there were large differences between the two sets of value, which was very unusual, we chose one or the other and gave reasons for our selection. Next one, slide.

So, this is an example of the criteria that were used in these different reports. There are two columns for IOM values, for EARs and for IOM and two for EFSA. And then here's on the last column, the decision that we made and the functional outcomes that were used in these reports. Next slide. Next slide.

So, here's an example of a table where we have the ARs for proteins, vitamins and minerals, for example, and at the top of each column, it tells you where the source of that nutrient value came from. Next slide.

We also estimate some of the ARs and what we did is essentially back calculated from the AI values. This is not statistically supposed to be done, but even Alicia Carriquiry, who's a world-class statistician said, "This is much better doing this, just subtracting something from the AI than not having anything at all, even though it probably overestimates requirements much better though, than using the AI or the RDA for estimating prevalence of inadequate intakes."

Another issue is that the AI is based on usual intakes of well-fed populations. So, that would also cause an overestimate. We showed in the tables, which ones were back calculated, and we didn't do it for young children except for iron, zinc and protein. Next slide.

We had bioavailability corrections for iron and zinc. These are pretty standard at this point, WHO, FAO, the Zinc Consultative Group have presented these, and these could be tweaked some more possibly. We say, "What is the usual phytate content of the use of your diet?" And you can choose which values to use. This is really the almost one and only modification that needs to happen globally is for bioavailability. Next slide.

We also developed harmonized upper levels using EFSA values and IOM values, mostly IOM, they're more recent, better explained. Hardly any in FAO, WHO, and there's a lot of inconsistent criteria for how these are developed, but we did explain our decisions. Next slide.

And the next slide shows the table that we came up with, with the values, showing a gang comparison of IOM and EFSA, and the decision that we used in the last column for the values and the criteria. Next slide.

So, to summarize the two slides, we now have a set of AR and UL values much larger than is currently available anywhere else. And there are a lot of money spent developing these. We haven't made them up from thin air they're, I would say, $20 million was spent, no, 30 million obtaining these values, euros and dollars. There's a very useful set of values now that we can use for evaluating intakes and programs and risk of excess intake and compare across countries and regions. And then countries can take these values and set their own dietary guidelines, and they have to do that based on their own target median intake and adjusting for bioavailability of iron and zinc. And these values can be obviously just modified locally as well. If people have objections for any reason. Last slide, I believe.

So, this is what Connie was questioning and I think is really important as a next step. Local adjustments to NRVs are really needed. We are assuming that's my small group that all humans share similar biology and requirements for absorbed nutrients. They can be one set of biologically based NRVs for the world, and then countries and regions should consider adjustments that they need for their population. So, bioavailability would be one, and there are algorithms available for doing that. That can be selected locally, iron and zinc, mostly. Body size and activity. Well for energy and protein, if you express the values per kilogram body weight, then you have dealt with the problem of people being different sizes. Genetics? Maybe. There are some polymorphisms that may be so prevalent that the absorption of the nutrient is impaired and higher intakes would be useful. They MTHFR polymorphism is one that stands out as being affecting 25% of the population in Latin America, for example.

Infection? Really, not everybody is infected. You shouldn't be just recommending higher intakes for the whole population, because some people have infections. You should be dealing with the infections and vitamin D always pops up, but that's a non-starter because for example, in the IOM and EFSA, they recommend enough vitamin D for everyone, because you just can't assume that people are getting enough from sunlight. So, you just make that a non-issue. So, the last thing is what next steps? I think it's really important to define and quantify those potential adjustments. And I'm studying a working group in ASN to do that.

What factors really affect requirements, and can we quantify those? Is it as simple as I'm laying out here or are there a lot more things we should consider? And then by how much should we adjust these NRVs in different situations, if at all. The National Academy is going to be working on implementation of the tool kit and training on the application of NRVs, how to use them, because these are tricky. We've had interesting conversations in developing these talks for this, for this meeting, and how do you really do this? How do you estimate requirements for a population group, and so on? I think a lot more training needs to happen along those lines. And that's my talk. Thank you very much. And I look forward to very much to hearing the other talks in this session. Thank you.