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Public Health Impacts of Substances Detected at Low Levels in Food:

A Workable Approach to Risk Management Decisions

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Impetus for Creating a Tool

- There are more and more low-level detections of substances in foods
  - Many lead to recalls or other product actions
- Many detected substances are poorly characterized from a toxicological perspective
  - Lack of knowledge may lead to misallocation of resources and inappropriate responses
    - Fear of the presence and assumed hazard of the substance, not from any health risk

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Impetus for Creating a Tool

- There are a number of papers in the literature explaining how to address low-level exposures.
- There are accepted regulatory approaches in place that deal with some low-level exposures.
  - Threshold of Regulation
  - Action Levels, Tolerances
- Some low-level detections result in problems while similar ones do not. Something is not connecting...

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Impetus for Creating a Tool

- The future does not look much better
  - Chemists will continue to find smaller amounts in more foods
  - Animal testing is under pressure, so less toxicology data will be generated
  - Resources for analysis and action will remain limited
  - Pressure to act quickly will continue to increase

- We need to find a way to avoid chasing after each “discovery” of a low level of a substance as if it is a problem.

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Technical Committee on Food & Chemical Safety

- Saw the need to expand the understanding that most low-level exposures are not significant public health issues in order to cover more substances being found in food, and do it in such a way that is reasonably simple understand and can be generally accepted.
  - Transparent and widely accepted concept and common process
    - To bridge the gap between science and actions
    - To give credibility to safety determinations based on exposure
  - Not intended to create something completely new
    - Based on peer-reviewed science and methods in the open literature

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Technical Committee on Food & Chemical Safety

- Preparing a draft paper outlining such an approach.
  - Not unlike the work done by ILSI Europe (Barlow et al., 2001; Kroes et al., 2004), but recommend a simpler method.
  - Still under construction
  - Once finalized, the approach will be reviewed and published
- Plan to disseminate the approach broadly with the help of GMA, IFIC, and others.
  - Want a common view that the TTC can be used in many situations of low-level exposure

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Technical Committee on Food & Chemical Safety's Findings

- There is a rich literature supporting the threshold of toxicological concern (TTC) as a sound scientific concept and this can be a useful approach to prudently handle low-level exposures.
  - Reviewed 20 or so papers
    - All stress its inherent conservatism
    - In particular, Kroes et al. (2004) very thoroughly compile the current thinking about TTC
  - Found nothing refuting the concept, the methods used, or the levels determined.

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Threshold of Toxicological Concern

- A 500-year-old concept
  - Paracelsus (c. 1508)
- A 50-year quest to apply it broadly
  - First mentioned by Ben Oser on behalf of the IOM's FPC (1958)
  - Many approaches using different toxicology data and (publications from 1967-2007)
  - FDA's Threshold of Regulation (1995)
  - JECFA for flavoring substances (1997)
  - ILSI Europe workshops (1999, 2003)
  - British Toxicology Society annual congress (2007)

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Scientific Underpinnings

- Thresholds exist
  - Level of exposure to a substance below which no significant risk is expected.
  - A unifying theme in regulatory toxicology (Cheeseman, 2005)
- By using distributions of thresholds determined for all reported substances and toxicologic endpoints in animals and highly conservative assumptions about applying them to humans, exposure levels can be derived below which there is insignificant public health concern.
  - A practical threshold for acceptable public health risk
  - Does not ensure zero concern, but reasonable certainty of no harm

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Applications of the TTC to Materials in Food

- Frawley (1967)
  - NELs from 220 chronic studies
  - Concluded 0.1 ppm in total diet (approx. 300 µg/d)
  - Intended for packaging; excluded metals and pesticides
- Flamm, Rulis et al. (1980s)
  - TD50s for 477 substances
  - Concluded 0.5 ppb in total diet (1.5 µg/d)
- Munro et al. (1996, 1999)
  - 613 organic chemicals and 2900 NOELs
  - Tiered approach based on Cramer et al.'s (1978) structural classification, resulting in TTCs of 90, 540, and 1800 µg/d
    - 18 µg/d for neurotoxic compounds (OPs; cholinesterase inhibition)

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Applications of the TTC to Materials in Food

- Cheeseman et al. (1999)
  - Tiered approach based on structural alerts, genotoxicity, and short-term toxicity data
  - Extends TOR from 0.5 to 5 to 15 ppb (1.5 to 15 to 45 ug/d)
- Barlow et al. (2001) and Kroes et al. (2002-5)
  - International teams refining the use
  - TTCs ranging from 0.15 – 1,800 µg/d

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Applications of the TTC to Materials in Non-food Items

- Expanding the application of TTC
  - Pharmaceuticals (Dolan et al., 2005)
    - Compounds likely to be carcinogenic – 1 µg/d
    - Compounds possibly potent or highly toxic – 10 µg/d
    - Compounds not likely to be the above – 100 µg/d
  - Consumer products (Blackburn et al., 2005)
    - Dermal exposure
    - Munro's use of the Cramer classifications suitable

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Technical Committee on Food & Chemical Safety's Findings

- TTC fulfills the criteria for "significant scientific agreement"
  - Qualified experts agree that the scientific evidence supports TTC
  - High level of confidence in its validity; the TTC is unlikely to be reversed by new science, although it may need to be refined as science evolves
  - It is objective (uses a body of sound and relevant scientific data)
  - It is flexible (recognizes the variability in the amount and type of data needed to support different substance-toxicity relationships)
  - It is responsive (can re-evaluate approach over time as research questions and experimental approaches change).
  - While significant scientific agreement does not require unanimous and incontrovertible scientific opinion, the TTC is close to it.

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Technical Committee on Food & Chemical Safety's Position

- The Threshold of Toxicological Concern is an established approach based on a wealth of toxicologic data. By applying conservative principles to extrapolate animal data to man, it can be used to determine at an early stage whether or not the presence of an unexpected material in food might have a meaningful public health impact.
- The TTC is not a "way out" for anyone. It needs to be applied prudently in order to protect the public in an accepted manner.

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Technical Committee on Food & Chemical Safety's Position

- Its use must be lawful and meet the criteria set forth below.
- It must be made simple enough for broad, common acceptance and practical use.

- Now is the time to implement the TTC as fully as possible as a suitable, conservative procedure to handle many low-level exposures, before systems become overwhelmed and our ability to differentiate priorities becomes lost in all the competing demands.

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Technical Committee on Food & Chemical Safety's Position

- Before formal risk ranking, prioritize concern based on estimated exposure and what is known about the chemical
  - Install a "Pass-Fail" system
  - Similar to triage used by emergency or medical personnel to ration limited resources when the number of injured exceeds what is available to provide care.
- Low-priority issues do not need immediate action because they are of negligible public health concern. Therefore, society can apply scarce resources, including risk assessment and ranking, to situations deserving them.

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TTC vs. Risk Ranking

- TTC
  - Set criteria for acceptable, negligible concern
  - Evaluate exposure to a chemical relative to its criterion
  - Can be applied without chemical-specific hazard data
- Risk Ranking
  - Rank relative to other substances/hazards
  - Consider chemical hazards + potential exposure

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Technical Committee on Food & Chemical Safety's Approach

- Determining whether a compound found in a food at a low level would or would not cause concern
  - Screen for applicability
  - Apply a simplified decision approach using values and methods in the literature.
    - Structural alerts will be considered
    - Use a minimum of exposure levels for which there is consensus.
      - 1.5 µg/d from Rulis; 15/18 and 90 µg/d from Cheeseman and Munro
      - For simplicity and conservatism, we prefer to use only the Cramer classification structure (1978) level giving the lowest TTC and not going through the 33-step process for most compounds.
      - For simplicity and conservatism did not use the higher TTC tier from Cheeseman or the lower one from Kroes

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Technical Committee on Food & Chemical Safety's Proposed Framework

- Screen to ensure the TTC concept can be applied
  - Use only when cGMPs, HACCP, FCC, etc. are being followed
    - Not a substitute for proper manufacturing procedures and procurement standards
    - Not an attempt to circumvent laws or regulations
    - Exposure must be stopped whenever possible to give added safety assurance
      - Work with supplier to stop using material in question
      - Switch suppliers
      - Change manufacturing practices
      - Change ingredients

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Technical Committee on Food & Chemical Safety's Proposed Framework

- Screen when NOT to use the TTC
  - When adequate toxicology data are available
    - TTC is not a substitute for applying data to the issue
    - However, it does give guidance on the significance of the risk
  - When the material is a steroid, metal, or protein
    - Consensus is these need risk assessment and ranking
  - When the compound is a highly potent carcinogen
    - For example, N-nitroso compounds, strained heteronuclear rings, alpha-nitrofuryl compounds, hydrazines, triazenes, azides, azoxy compounds, polycyclic amines
      - From Cheeseman et al. (1999)

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Technical Committee on Food & Chemical Safety's Proposed Framework

- When the chemical passes the initial screen, start by looking for structural alerts
  - Beyond the potent carcinogens, for the purposes of the TTC, the functional groups identified by Ashby and Tennant (1988, 1992) and Tenant, et al. (1980) as showing evidence of reactivity to DNA will serve as the first step.
    - These are described in Munro et al. (1999).
  - A very comprehensive list that overlaps with the highly potent carcinogens; most would never be near food.
  - Chemicals with structural alerts can be either excluded from the TTC evaluation or given consideration based on genotox data.

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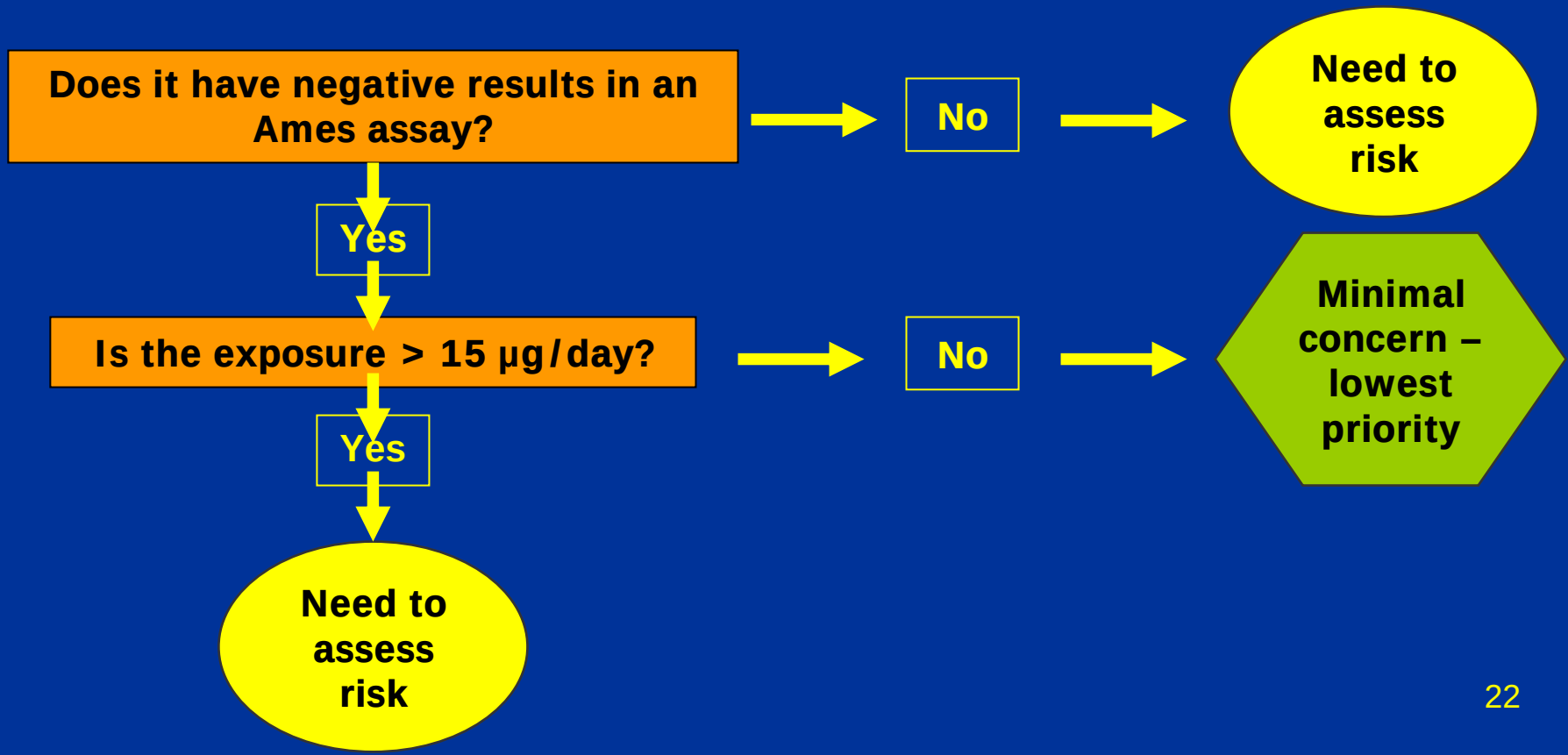
Technical Committee on Food & Chemical Safety's Proposed Framework

- Step 1: If there are structural alerts for genotoxicity



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- If there are no alerts, start by applying the default value of 1.5 µg/d
  - Based on work of Rulis, Flamm and others, and as applied in the Threshold of Regulation
  - Widely accepted as highly conservative and protecting against all hazards, including cancer
- As more data about the structure of the compound are generated, the base level can be raised using the basic tenets of toxicology.
  - As structure and toxicity become less of a concern, threshold levels increase.

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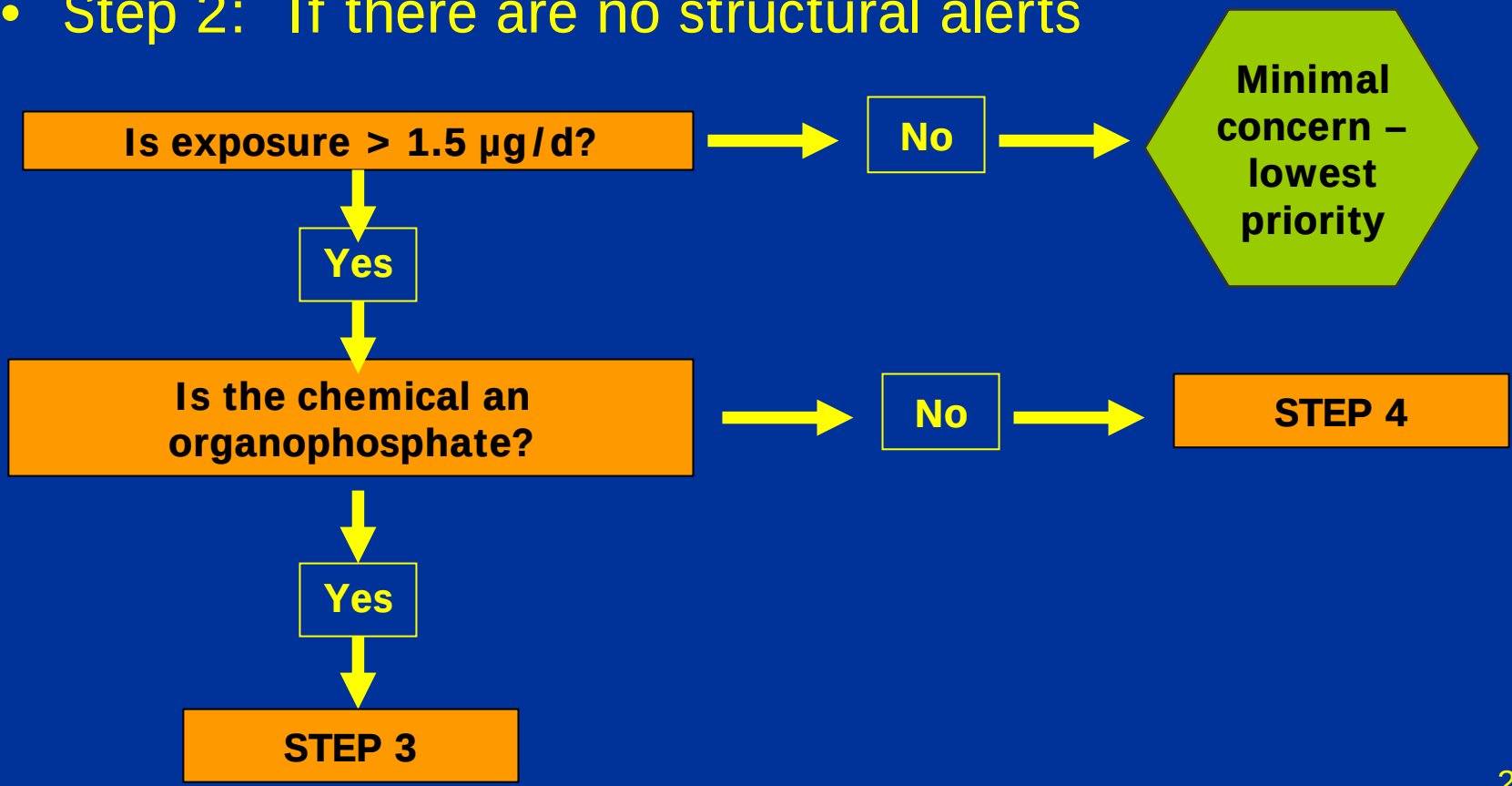
- Step 2: If there are no structural alerts



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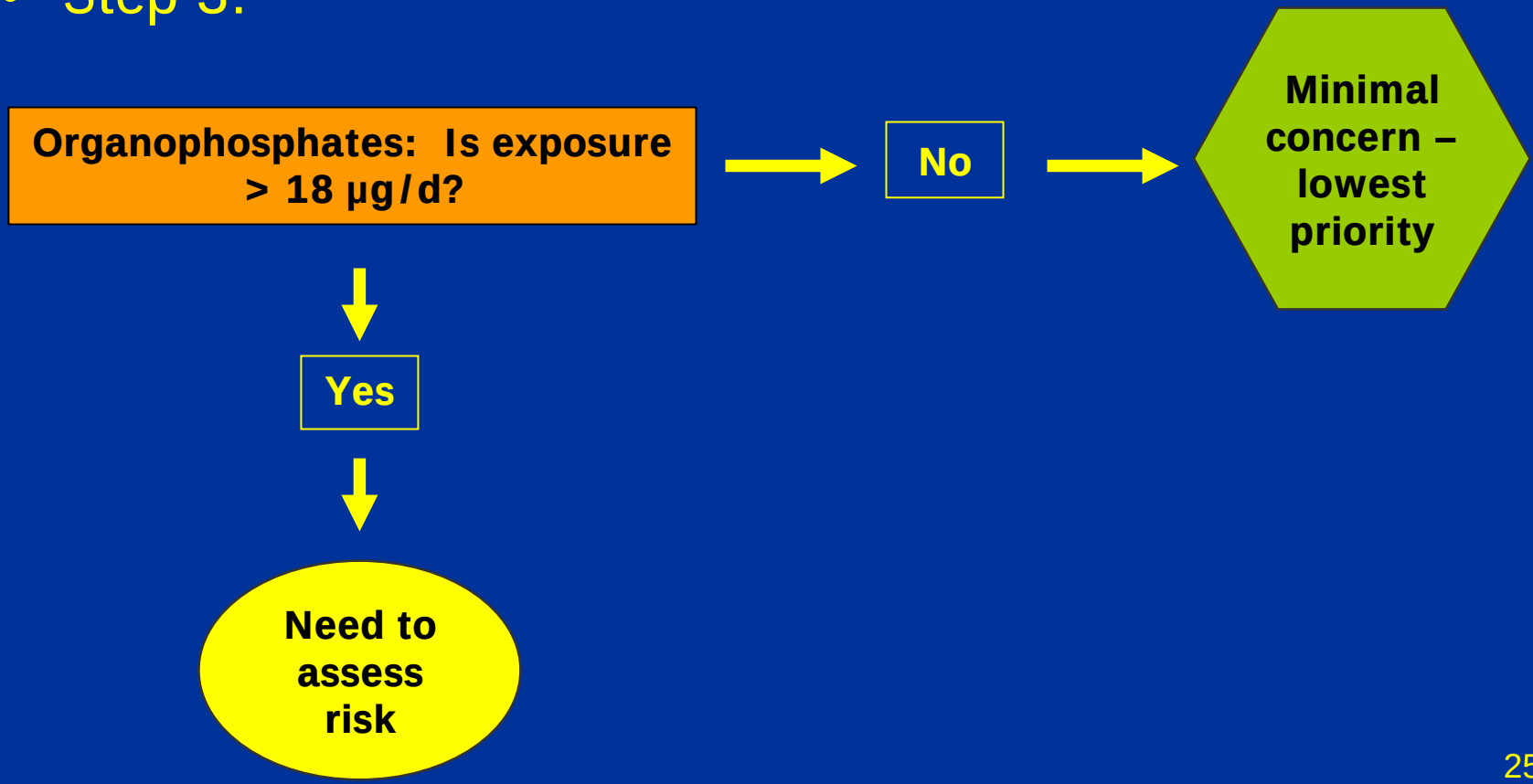
- Step 3:



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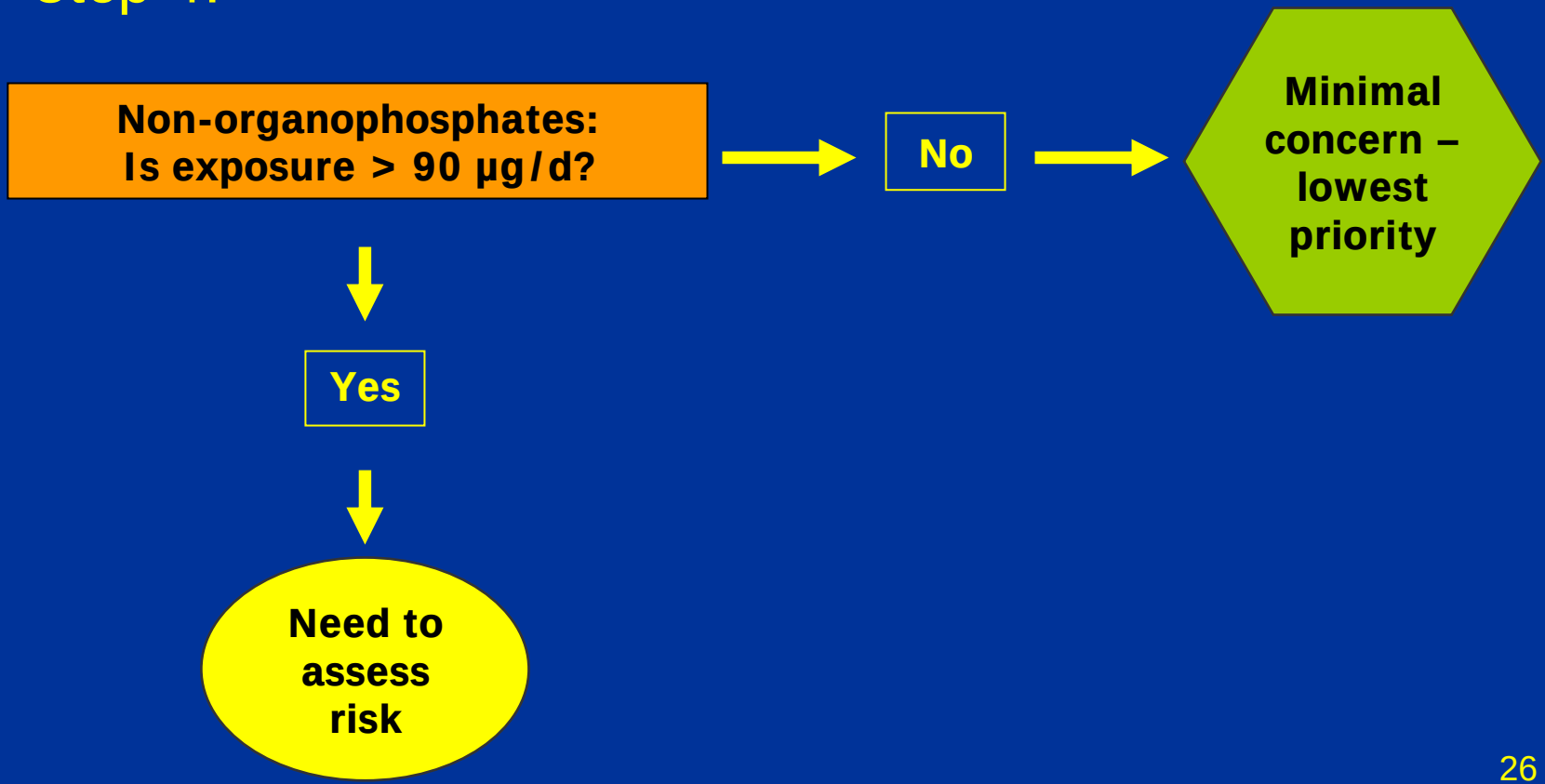
- Step 4:



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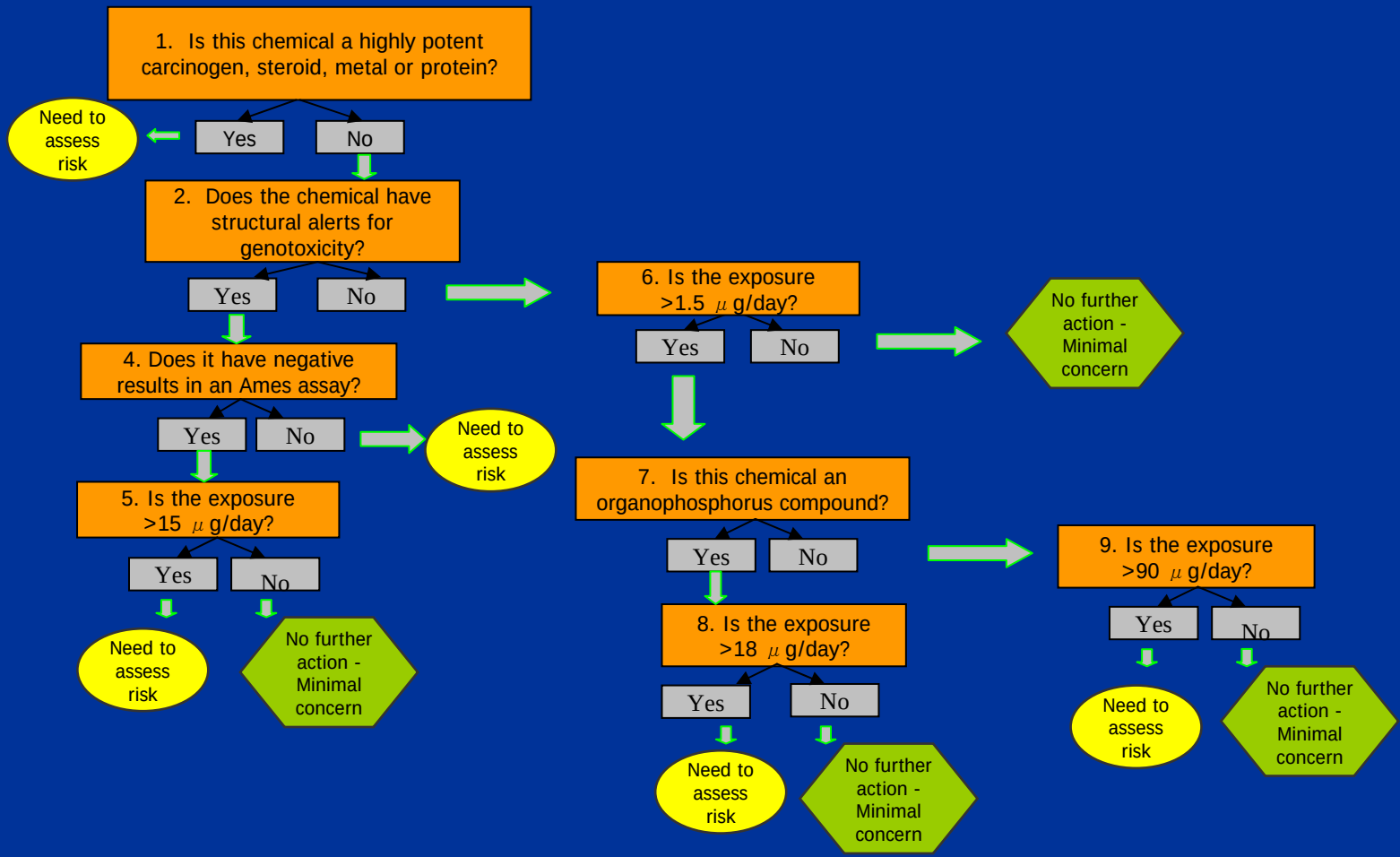
The Full Picture



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Conclusions

- Some materials do not fit into the TTC at this time and the foods that contain them need a formal risk assessment and ranking, or product action.
- If material is suitable for the TTC approach and the exposure is *less than* the identified level for the type of compound, then there is negligible public health concern and the situation goes to the bottom of the work pile.
  - Still need to correct the situation, but as long as prudent, meaningful steps are being taken, there is no need to take immediate or aggressive product action
  - No need for risk ranking

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Conclusions

- If material is suitable for the TTC approach and the exposure is *more than* the identified level for the type of compound, then there is likely a public health concern and the situation needs formal risk assessment and application of the risk ranking tools discussed at this workshop. Product action is likely.

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Future Work for the Committee

- Refine approach and submit it for publication.
- Develop a quick, reasonable way to perform an initial estimate of exposure.
- Work with GMA/FPA to show the legal basis for a broader application of the TTC concept in the US.
- Work with trade associations and other groups to gain broad acceptance.
- Work with regulatory agencies here and abroad to apply the TTC to more situations in a harmonized fashion.

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Summary

- A common understanding of the significance of low-level detections to public health is needed so everyone's resources can be applied appropriately.
- The TTC is a method of analyzing thresholds for all tested substances and toxic endpoints, and by using highly conservative assumptions to apply them to humans can derive exposure levels below which public health concerns will be minimal.
- The TTC is has been developed over 40 years with modifications and improvements, but no dissent.

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Summary

- Technical Committee on Food & Chemical Safety believes the TTC fulfills the criteria for significant scientific agreement.
- Technical Committee on Food & Chemical Safety reviewed the literature and distilled the various approaches into a practical, easy-to-use decision tree.
  - A lot of what is in the literature is not easy to apply during a "situation."
  - Improves transparency and ease of understanding, which should lead to broad acceptance and use.

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Summary

- Knowing exposure, and with little or no data on the chemical nature of the substance or its hazards, decisions about “situations” can be made easily that will responsibly protect public health.
  - As more information becomes available, can refine levels
  - Since risk is not zero, want to reduce or remove exposure whenever reasonably possible
- When concern is determined to be minimal, there is no need to formally assess risk or apply risk ranking.
  - Provides an approach to put some low-level exposures at the end of the queue and will allow some of us to go home on time.

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