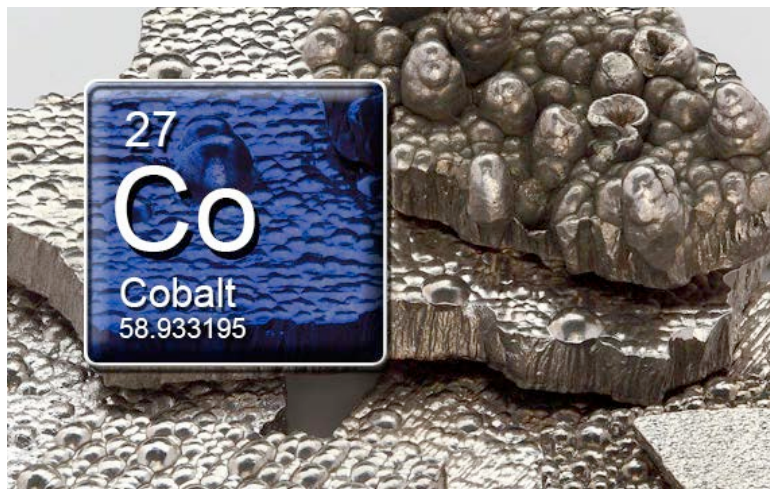


Process for Preparing the Draft RoC Monograph



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Office of the Report on Carcinogens

National Institute of Environmental Health Sciences

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Outline

Background on Report on Carcinogens (RoC)

Process for reviewing cobalt for the RoC

Protocol for preparing the RoC monograph on cobalt

How conclusions and the preliminary listing recommendation were reached

Peer-review charge

Next steps



The Report on Carcinogens (RoC) is congressionally mandated

- Public Health Service Act, Section 301(b)(4) (1978, amended 1993)
 - Directs Secretary, Health and Human Services (HHS) to publish a list of carcinogens
 - Lists substances as “*known*” or “*reasonably anticipated human carcinogens*”
- Identifies substances that pose a cancer hazard for people in the United States
- NTP prepares the RoC for the Secretary, HHS
- Each edition of the report is cumulative





Process for the Preparation of the RoC

Nomination and Selection of Candidate Substances



Scientific Evaluation of Candidate Substances



Public Release and Peer Review of Draft RoC Monographs



HHS Approval and Release of Latest Edition of the RoC

Invite nominations to the RoC

Interagency review

Public comment

Develop draft concept documents for substances proposed for evaluation

Public comment

Review of draft concept documents by NTP Board of Scientific Counselors*

(**public meeting, public comment**)

NTP Director

Select candidate substances

Prepare draft RoC Monograph for a candidate substance (initiate cancer evaluation component)

External scientific input, as needed

(e.g., consultants, *ad hoc* presentations, expert panels*)

Public input

(e.g., listening session, comment)

Interagency input

(complete cancer evaluation component and prepare draft substance profile)

Interagency review

Complete draft RoC Monograph

Release draft RoC Monograph

Public comment

Peer review of draft RoC Monograph by NTP Peer-Review Panel*
(**public meeting, public comment, peer-review report**)

Present information regarding the peer review and revised draft RoC Monograph to NTP

Board of Scientific Counselors
(**public meeting, public comment**)

NTP Director

Finalize RoC Monograph (cancer evaluation component and substance profile)

Submit recommended listing status for newly reviewed candidate substances

NTP Executive Committee

Approval of listing status by Secretary, HHS

(transmit latest edition of RoC to Congress and release to the public)

Key

HHS = Health and Human Services

NTP = National Toxicology Program

RoC = Report on Carcinogens

* Federally chartered advisory groups



Process for Reviewing Cobalt for the RoC

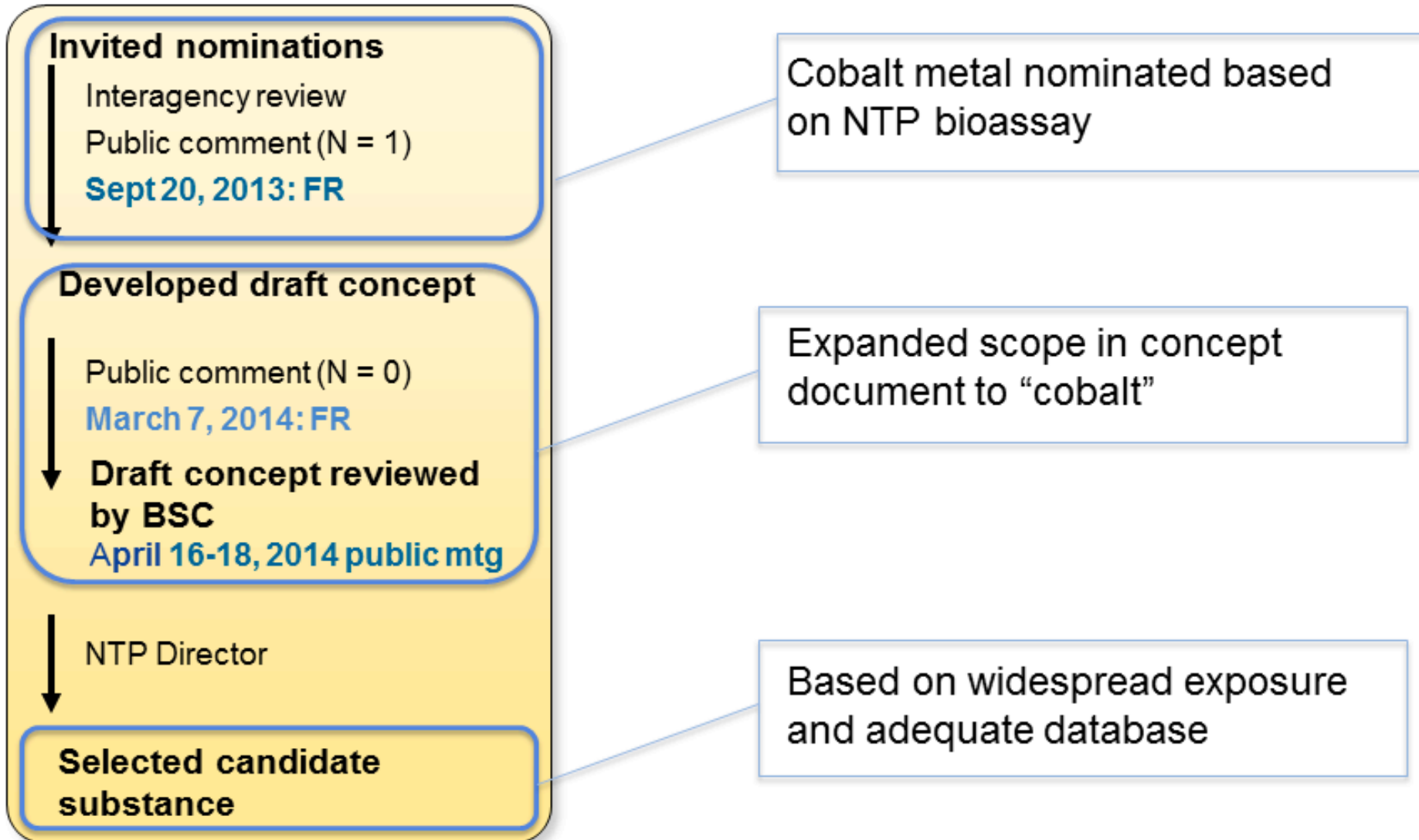
RoC related products

- Concept document
 - Contains rationale and proposed approach for the substance review
- Draft RoC monograph consists of two parts
 - Cancer hazard evaluation component
 - Substance profile
- Report on Carcinogens
 - Compilation of substance profiles for each listed substance



Completed Steps in the Process

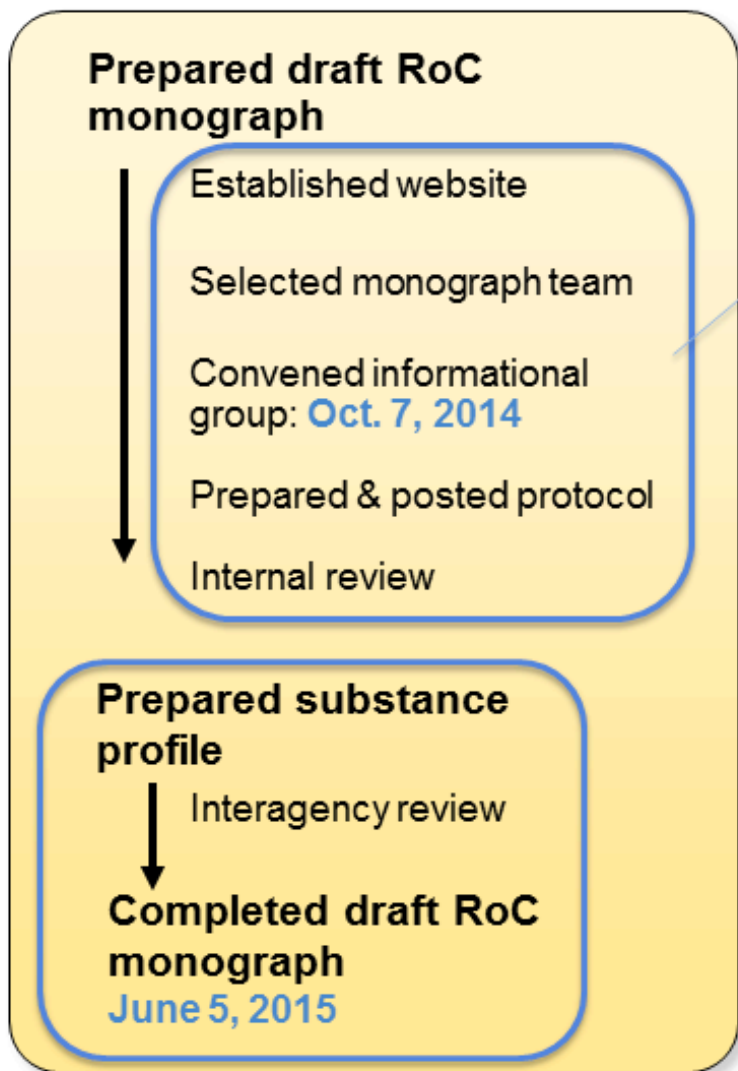
Selection of “cobalt” as a candidate substance





Completed Steps in the Process

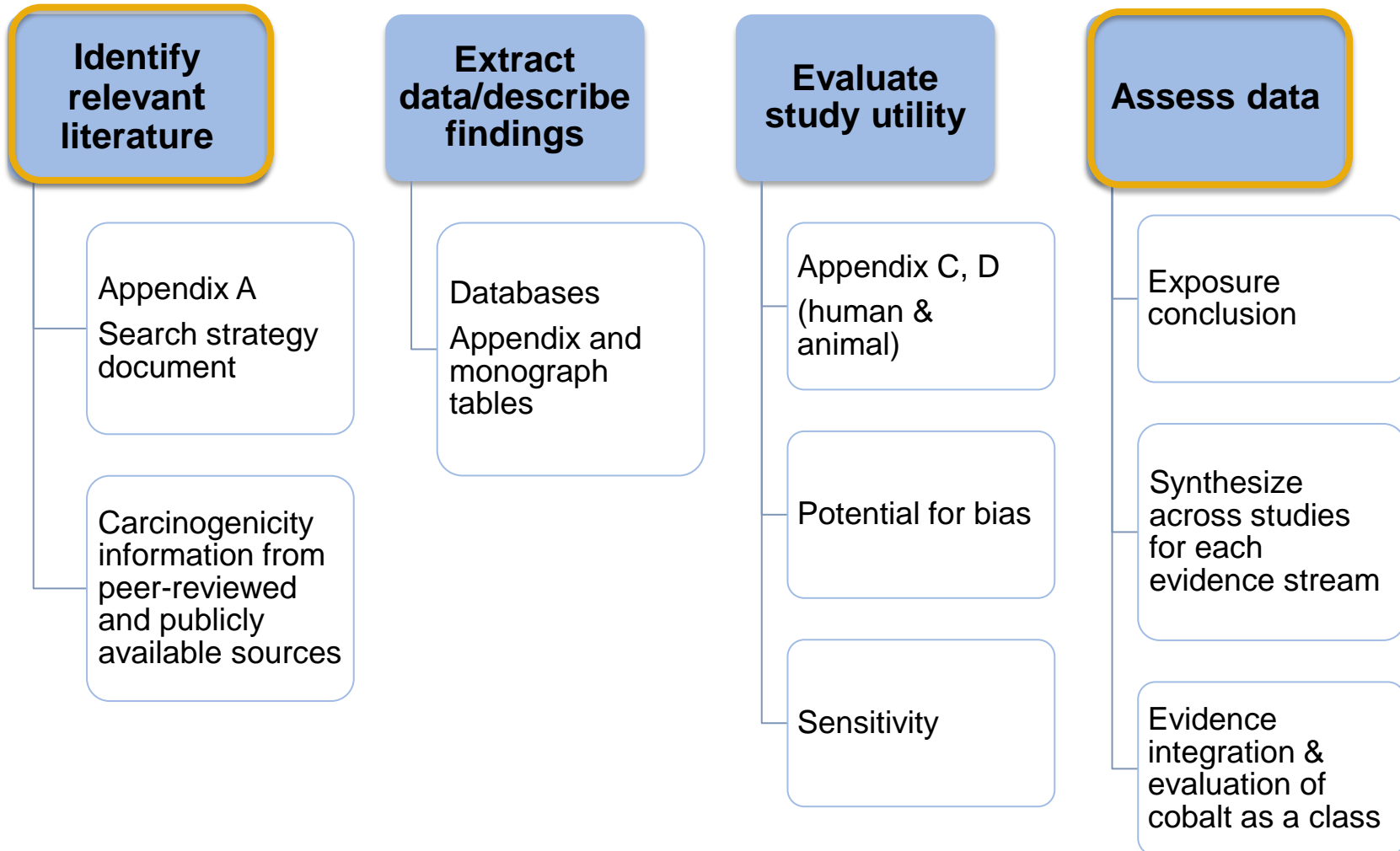
Candidate substance defined as the class – cobalt and certain cobalt compounds (cobalt*)

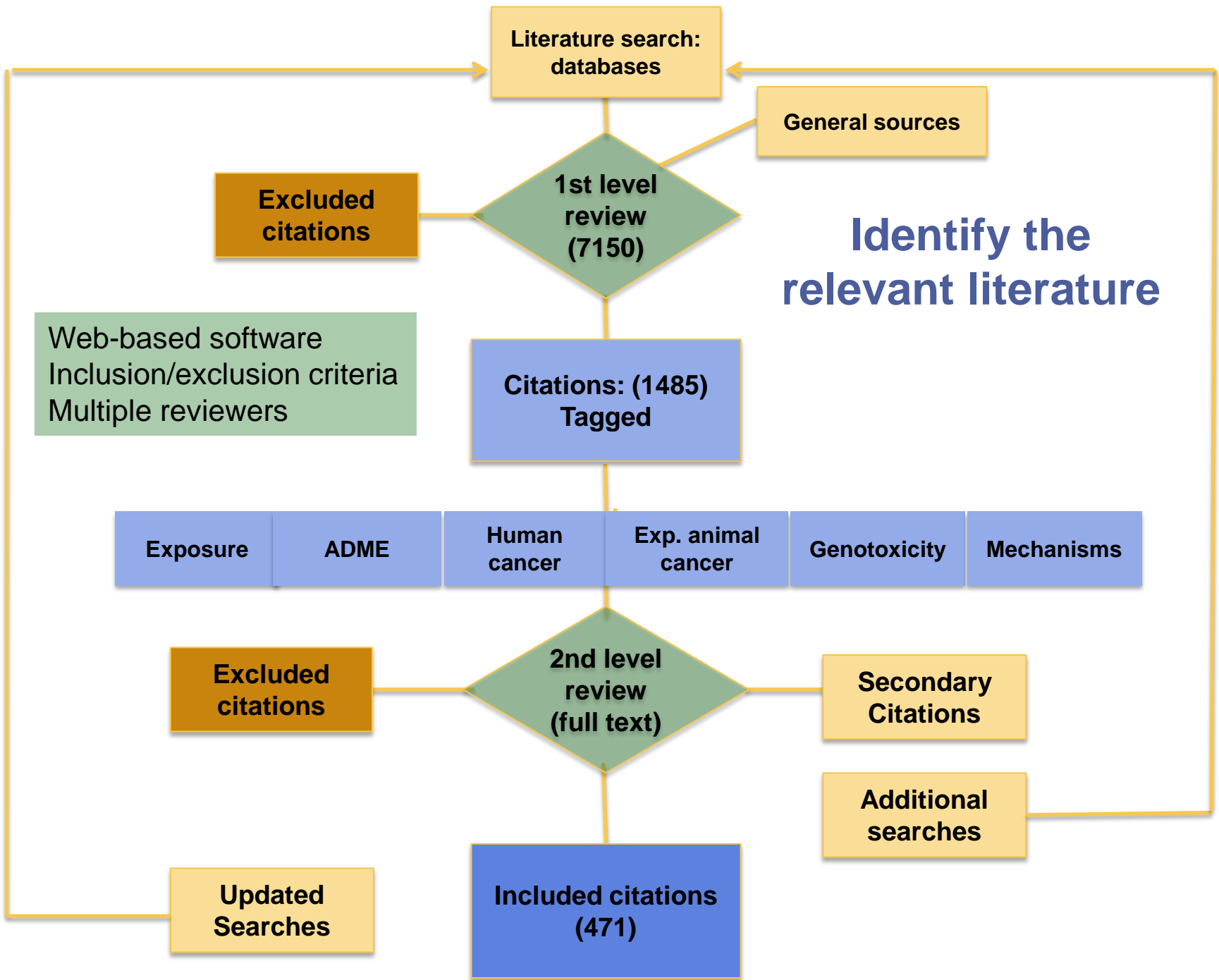


- “Certain” refers to those cobalt compounds that release cobalt ions *in vivo*
- Agreed with concept document to exclude cancer studies on cobalt alloys and radioactive cobalt because of concerns of confounding
- Proposed class based on mechanistic data
- Cobalt sulfate, which is currently listed in the RoC, is included in the evaluation
- Other metal compounds in the RoC are listed as a class rather than as individual compounds



Protocol for preparing the cancer hazard evaluation





Identify the relevant literature

Web-based software
Inclusion/exclusion criteria
Multiple reviewers

- Exposure
- ADME
- Human cancer
- Exp. animal cancer
- Genotoxicity
- Mechanisms



Reach RoC Conclusions

Evaluate whether a significant number of U.S. residents are exposed to cobalt*

Congressional mandate

- Publish a report that lists substances which are *known* or *reasonably anticipated to be human carcinogens* **and to which a significant number of persons residing in the United States are exposed**

Evaluate data

- Exposure usually inferred from data on use, production volume, occupational monitoring, environmental (occurrence), estimated intake, and biomonitoring
- Past exposure is relevant because cancer has a long latency period

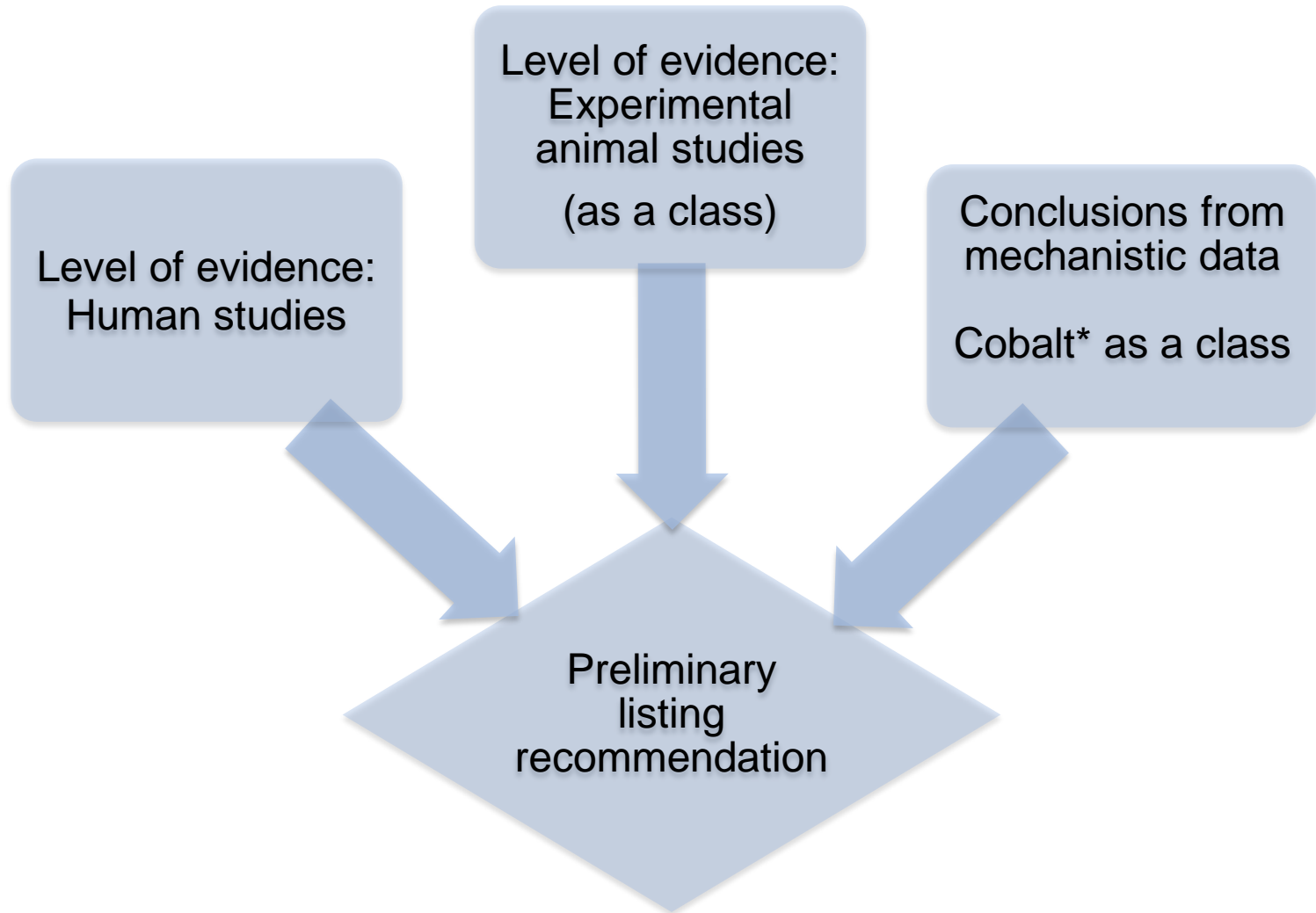
Reviewer instructions

- Use their judgment as to whether the exposure information in the draft monograph supports NTP conclusion that a significant number of U.S. residents are exposed to cobalt*



Reach RoC Preliminary Listing Recommendation

Evaluate evidence for carcinogenicity of cobalt*





Reach level of evidence conclusion for carcinogenicity from studies in humans*

Sufficient evidence

- Causal relationship between exposure to the agent, substance, or mixture, and human cancer

Limited evidence

- Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.



Reach level of evidence conclusion for carcinogenicity from studies in experimental animals

Sufficient evidence

- Increased incidence of malignant and/or a combination of malignant and benign tumors
 - In multiple species or at multiple tissue sites
 - By multiple routes of exposure
 - To an unusual degree with regard to incidence, site, or type of tumor, or age at onset



Evaluate mechanistic and other relevant data

- Provides context for biological plausibility of findings reported in human and experimental animal cancer studies
- Mechanistic data are often sparse
- Can be used to list/not list a substance or support findings in humans and experimental animals
 - Agent belongs to a well-defined, structurally related class of substances whose members are listed in the RoC
 - Convincing data that a substance operates by a mechanism that would cause cancer in humans
 - Compelling data that a substance causes cancer by a mechanism that would not occur in humans
- Evaluate evidence for considering cobalt as a class



Reach preliminary listing recommendation

Known to be a human carcinogen

- Sufficient evidence of carcinogenicity from studies in humans

Reasonably anticipated to be a human carcinogen

- Limited evidence from studies in humans
OR
- Sufficient evidence from studies in experimental animals
OR
- Less than sufficient evidence in humans or experimental animals
 - Agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous RoC as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen
OR
 - Convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans



Guidance (final paragraph of criteria)

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information.

Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance.

For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.



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Charge

To comment on the draft cancer evaluation component, specifically, whether it is technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria

To comment on the draft substance profile, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of cobalt and certain cobalt compounds

Actions (votes)

Whether the scientific evidence supports the NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in human and experimental animals of cobalt and certain cobalt compounds

Whether the scientific evidence supports the NTP's preliminary listing decision for cobalt and certain cobalt compounds in the RoC



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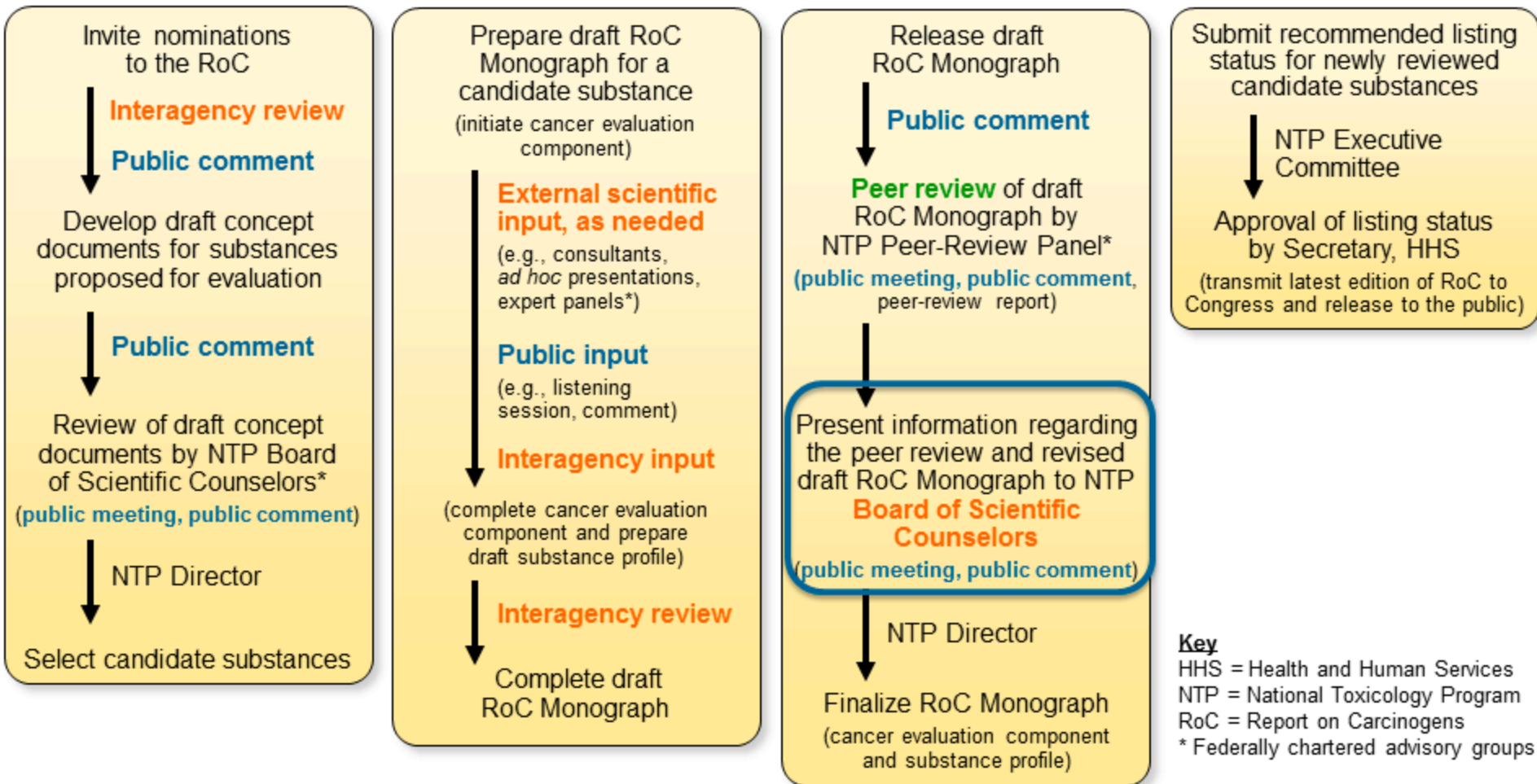
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Questions?