GUIDANCE FOR IMMUNOTOXICITY RISK ASSESSMENT FOR CHEMICALS

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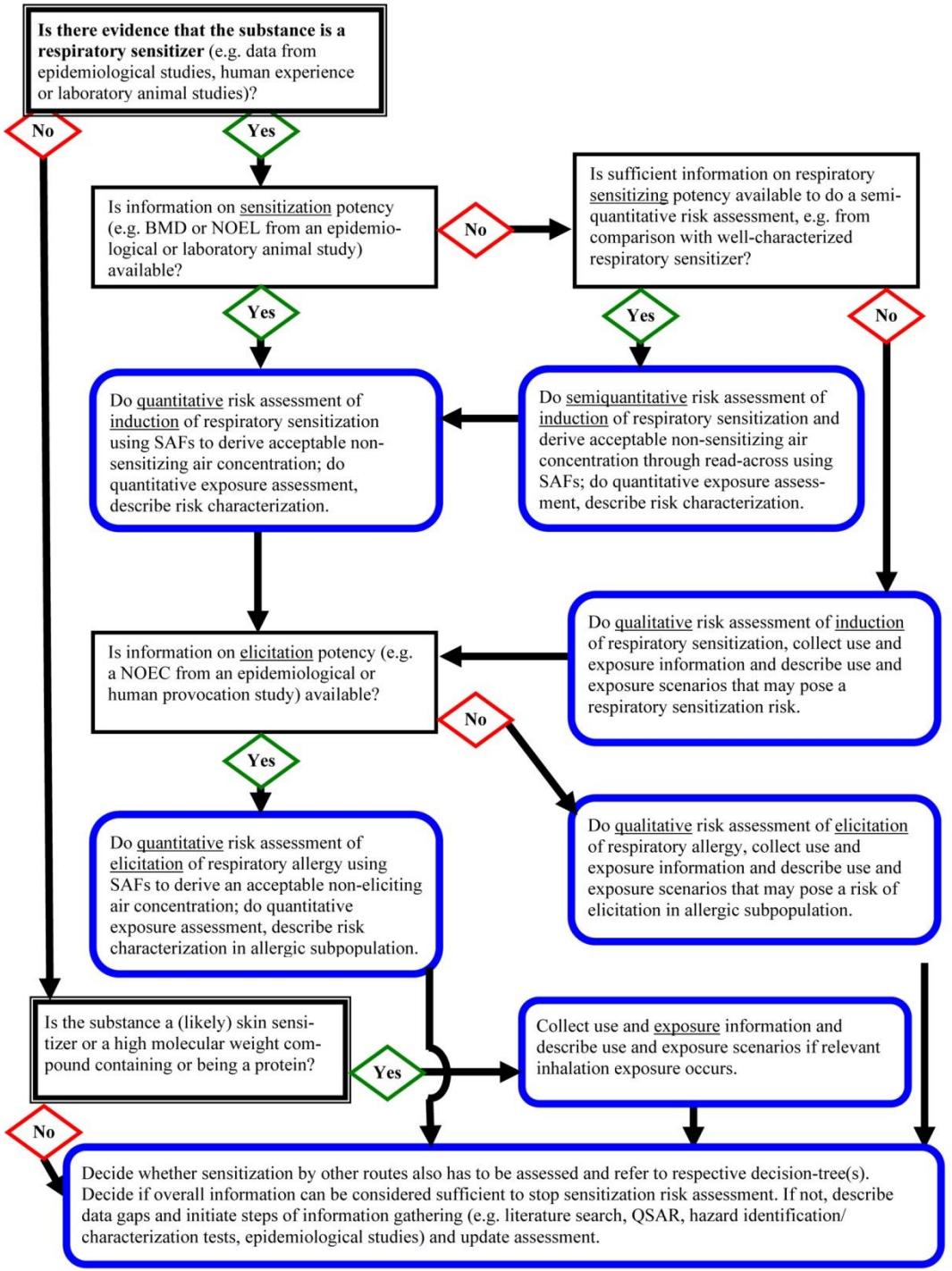
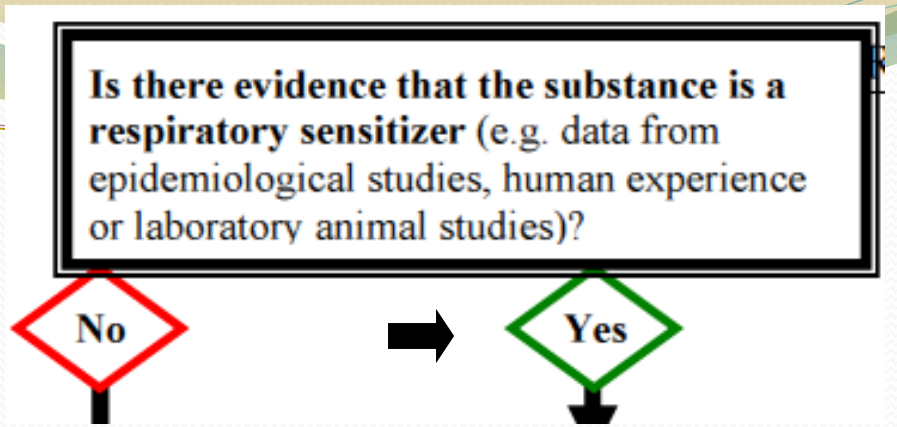
Generic Decision Tree for Respiratory Sensitizers



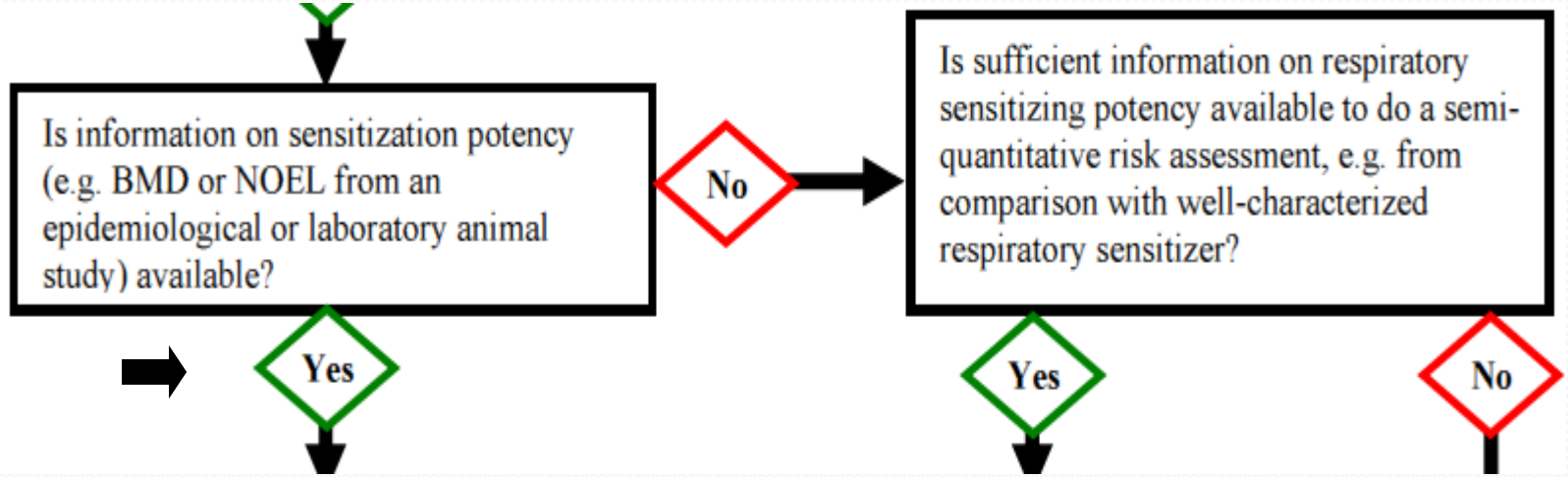
Assessment of sensitization and allergic response to halogenated platinum salts –Case Study 3

Respiratory sensitizer?



- numerous occupational studies report allergic reactions following exposure to soluble halogenated Pt salts (refs in WHO, 2010, 2012)
  - Respiratory symptoms: airway constriction and inflammation, shortness of breath, wheezing, rhinitis (runny nose and sneezing)
  - conjunctivitis (burning and itching eyes)
  - urticaria (hives)
  - dermatitis (itching skin eruptions)

Potency data?



- Occupational studies: increased prevalence of workers with respiratory allergy at estimated workplace air concentrations below 2 µg sol. Pt/m³

Potency Data - Occupational Studies

- Baker (1990) and Brooks (1990)
  - LOEL & exposure-response unclear
  - NOEL was not identified
- Bolm-Audorff (1992)
  - exposure data are not quantitative
  - NOEL & exposure-response relationship not identified
- Linnett (1999)
  - NOEL & exposure-response relationship not identified
- **Merget (2000)***

Potency Data – Occupational Studies

- Merget (2000)
  - 5-year prospective study in German catalyst production plant
  - sensitization indicated by positive SPT to H_2PtCl_6
  - exposure categories (high, low, and no exposure) based on job classifications
  - Air monitoring data for soluble Pt reported by category
    - stationary samples (1992-1993), personal samplers (1993) for high exposure only
    - arithmetic mean across both years used

Potency Data – Occupational Studies

- Merget (2000)

Exposure Group	Mean Conc. (ng sol. Pt/m³)	Incidence of skin prick
High	53 ± 20	13 /115
Low	3.4 ± 0.8	0 / 111
No	0.0048 ± 0.005	0 / 48

Suitable data for quantitative risk assessment

NOEL for respiratory sensitization: 3.4 ng sol. Pt/m³

Potency Data – Animal Studies

- Biagini (1986)
  - Inhalation exposure of monkeys to $[NH_4]_2PtCl_6$ causes respiratory sensitization
    - in 1/8 monkeys exposed to Pt alone
    - in 4/8 monkeys exposed to Pt + ozone
    - in 0/7 monkeys exposed to ozone alone

    inadequate for deriving exposure-response relationship

    support observation of sensitization from soluble halogenated Pt compounds in workers

Derivation of Acceptable Exposure Level

- NOEL 3.4 ng sol. Pt/m³
- Uncertainty factors

interspecies	1	human data
intraspecies	10	default, no definitive data
matrix	1	air
use		not relevant
time	10	if assessing chronic exp.
database	1	not required, several supporting studies

- AEL (workplace) 0.034 ng sol. Pt/m³

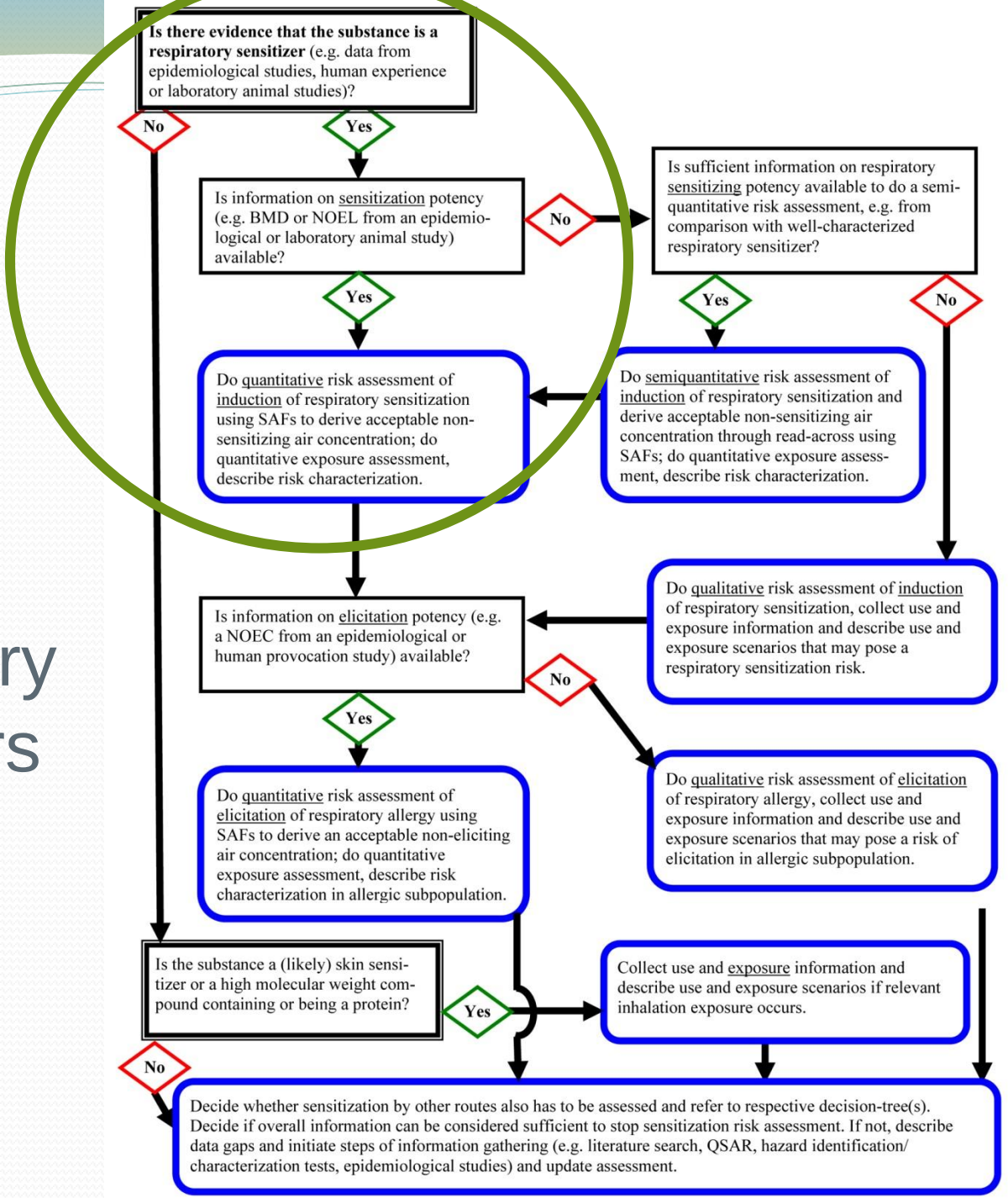
Derivation of Acceptable Exposure Level

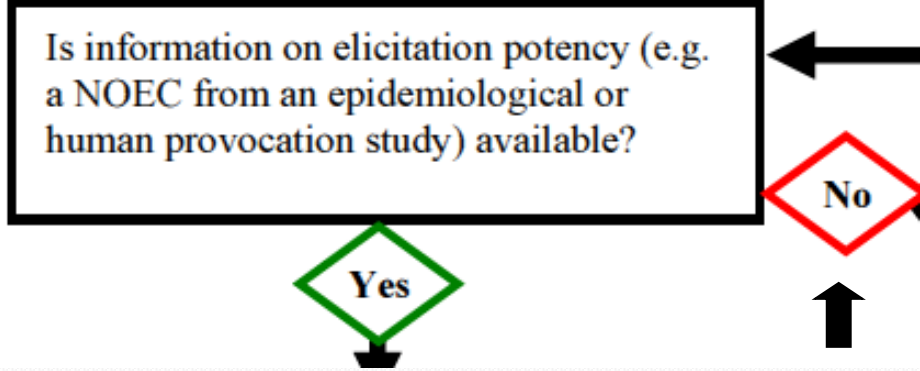
- NOEL : 3.4 ng sol. Pt/m³
- Adjustment for lifetime vs occupational exposure

$$NOEL_{adj} = NOEL \times \frac{\text{daily resp. vol.}}{10\ m^3/d / 20\ m^3/d} \times \frac{\text{working days}}{5\ d / 7d}$$

- $NOEL_{adj}$: 1.2 ng sol. Pt/m³
- Uncertainty : 100 (for sensitization)
- Reference value (sensitization): 0.012 ng sol. Pt/m³

Generic Decision Tree for Respiratory Sensitizers





Elicitation data?

- Few human provocation studies (Merget 1996)
  - reduction of specific airway conductance by 50%: (10^{-2}-10^{-6} mol $PtCl_6^{2-}/m^3$, 10 breaths)
- Positive skin prick test in sensitized workers
  - still working: wide range (10^{-3}-10^{-8} g/mL)
  - terminated for allergy: lower mean (10^{-6} g/mL) and higher Pt specific IgE (Brooks 1990)

➡ Not sufficient quantitative elicitation information, qualitative description of exposure scenarios and concentrations that may lead to allergy elicitation

Exposure assessment

- Known relevant exposures
  - workplace
  - environmental form car catalytic converters (near streets 4-112 pg Pt/m^3 with small percentage of halogenated Pt (≤1%) (Merget 2001)
- Exposure measurement
  - personal vs. stationary air sampling
  - metal speciation: total soluble Pt measured, while specific immune reaction is against halogenated Pt complexes

Respiratory Sensitization Risk Characterization

- Reference value considered to carry negligible risk of sensitization to halogenated Pt compounds
- Relevant exposure restricted to Pt refinery and catalyst production workers
- Appraisal of toxicological information
  - good quality prospective cohort study
  - limited dose-response information as only one dose level with effects
  - considerable number of supporting studies

Respiratory Sensitization Risk Characterization

- Uncertainties
  - no measurement of halogenated Pt species, no personal samplers
  - unknown relevance of peak vs. mean Pt concentrations
  - Skin prick test detects only IgE-mediated type 1 allergic responses, but may miss non-IgE mediated hypersensitivity found in ~10% on sensitized workers

Respiratory Sensitization Risk Characterization

- Groups at risk
  - asthmatics and individuals with changes in airway integrity might be at an increased risk
  - co-exposure to irritants may increase sensitization risk
    - e.g. odds ratio higher in smokers than non-smokers (Merget 2000)
    - ozone in monkeys (1/8 w/o vs. 4/8 w ozone) (Biagini 1986)

Conclusions

- WHO Guidance on assessment of potential sensitization and allergic response
  - Includes decision tree (covered here)
  - Read document to learn more about
    - Possible ways to develop a POD
    - Uncertainty factors
    - Justification for approach
    - Weight of evidence
    - Also see Selgrade et al., Regulatory Toxicology and Pharmacology 63 (2012) 371–380
- Case study illustrates
  - Quantitative risk assessment is possible
  - Many examples would take you down the right side of the decision tree.