Comments on EFSA's scientific draft opinion on acrylamide in food

Janneke Hogervorst
Dept. of Epidemiology
Maastricht University
EFSA public consultation
Dec 10 2014

Comments

- Uncertainty in risk assessment:
  major, not moderate
  (page 186)

- Recommendations on research needs
  (page 192)
  - cancer risk
  - neurological disease risk / cognitive development
  - cardiovascular disease risk

EFSA draft scientific opinion AA in food

Risk characterization based entirely on rodent data

Conclusions:

- Neoplastic effects: MOE indicates concern
- Non-carcinogenic effects: MOE indicates no concern
- Level of uncertainty in risk assessment: moderate

Epidemiological data considered inconsistent and biological plausibility unclear > discussed but not used in RA

Ovarian cancer

2 studies show statistically significant positive association:

- Netherlands Cohort Study (stronger in never-smokers) (Hogervorst 2007)
- Nurses' Health Study (in normal-weight women and for serous ovarian cancer) (Wilson 2010)

Meta-analysis Pelucchi, Nov 2014:
Relative risk never-smokers: 1.39
95% CI: 0.97-2.00

Nurses' Health Study: no association between AA and GA Hb adducts and ovarian cancer risk (Xie 2013)

Hb adducts

Hb adducts: no gold standard for assessing long-term dietary AA exposure

- Large intra-individual variation
- Influence of incidental high exposures
- Expressed per g hemoglobin
- "Low association between the AA-adduct levels and questionnaire data points towards short-comings of both methods" (Vikström, 2012)

Studies correlating questionnaire data with Hb adduct data should not be called "validation studies" (page 185)

Endometrial cancer

3 studies show statistically significant positive association:

- Netherlands Cohort Study: only in never-smokers) (Hogervorst 2007)
- Nurses' Health Study (Wilson 2010)
- not in draft RA: European Prospective Investigation into Cancer and Nutrition: only in never-smokers and non-users of OC (Obon-Santacana 2014)

Meta-analysis Pelucchi, Nov 2014:
Relative risk never-smokers = 1.23
95% CI: 1.00-1.51

NTP 2012: endometrial hyperplasia in rats

Kidney cancer

1 study shows statistically significant positive association:

- Netherlands Cohort Study (Hogervorst 2008)

3 other out of 5 studies in total show increased risk

Meta-analysis Pelucchi 2014:
Relative risk = 1.20
95% CI: 1.00-1.45

Biological plausibility cancer

Norwegian BraMat cohort
(Hochstenbach 2012)
Male newborns:

- Pos. correlation cord blood AA-Hb and GA-Hb and micronuclei
  0.75 + 0.73 (non-smoking mothers)
- Pos. correlation gene expression wnt pathway

Taiwanese cross-sectional study
(Lin 2013)

- Positive association urinary AAMA and 8-OHdG in non-smoking adolescents

Biological plausibility cancer (continued)

Nurses' Health Study
(Hogervorst 2013)

- Some associations AA intake and sex hormones but no clear picture

Netherlands Cohort Study
(Hogervorst)

- Preliminary data: association between acrylamide intake and endometrial cancer risk modified by SNPs in CYP2E1

Acrylamide and birth outcomes

Prospective mother-child cohort
(Denmark, UK, Greece, Norway, Spain)
(Pedersen 2012)
Inverse association cord blood AA and GA-Hb and:

- Birth weight
- Head circumference

Norwegian prospective mother-child cohort
(Duarte-Salles 2013)

- Inverse association AA intake and birth weight
- Positive association risk small for gestational age

Back to EFSA draft RA

Epidemiology:

- Not consistent (cancer)
- Limited evidence for biological plausibility

But

✓Multiple good quality studies show positive associations

✓ Null findings do not negate positive findings

✓ Measurement error in AA does not lead to false-positive findings, but false-negatives, (RR in direction of null)

But….

- ✓ Studies with positive findings seem better suited to study association acrylamide and cancer (should be discussed in EFSA RA)

- ✓ Pelucchi meta-analysis, Nov 2014: "A modest association for kidney cancer, and for endometrial and ovarian cancers in never-smokers only, cannot be excluded"

- ✓ Some (limited) human evidence for biological plausibility

Perhaps too early to base risk assessment on, but should at least be appreciated in assessment of uncertainty

Uncertainty

If true, cancer and developmental toxicity risks much higher than estimate based on rodents

Table 31 draft RA:
+/- as given for uncertainty related to inconsistency human studies on cancer should be –

Table 31 draft RA:
how about uncertainty related to developmental effects? (2 positive studies on birth weight in humans: if true, MOE for dev. tox. is 1)

The uncertainty in EFSA risk assessment is not moderate but major

Research needs

Epidemiological studies

- Cancer risk: why not in draft RA?
- Birth outcomes
- Biological plausibility/causality, e.g., polymorphisms modifying risk (e.g., CYP2E1)
- Cardiovascular effects (Toker, 2013, see page 108 of EFSA report, oxidative stress)

Research needs (continued)

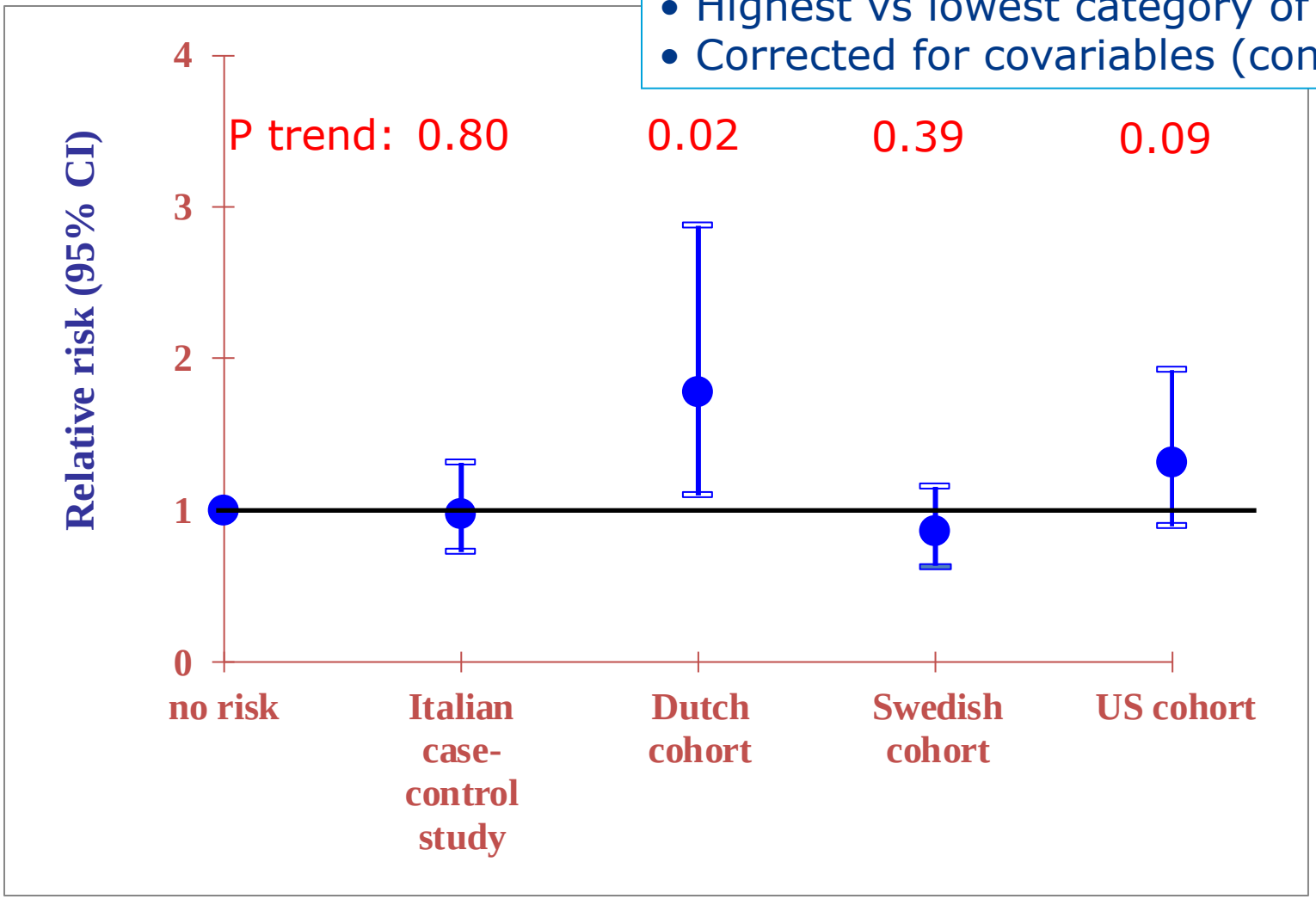
- Neurotoxic effects (e.g., dementia, cognitive development): not in draft RA

✓ AA affects both PNS and CNS
✓ Accumulation of AA to cys adducts in CNS
✓ Nerve degeneration
✓ Cumulative
✓ No regeneration of damaged neurons in CNS
✓ Animal models are no good models for human neurotoxicity in terms of cognition, behaviour
✓ Inverse association head circumference
✓ Other researchers recommend research on neurotoxicity: El Sayyad, LoPachin

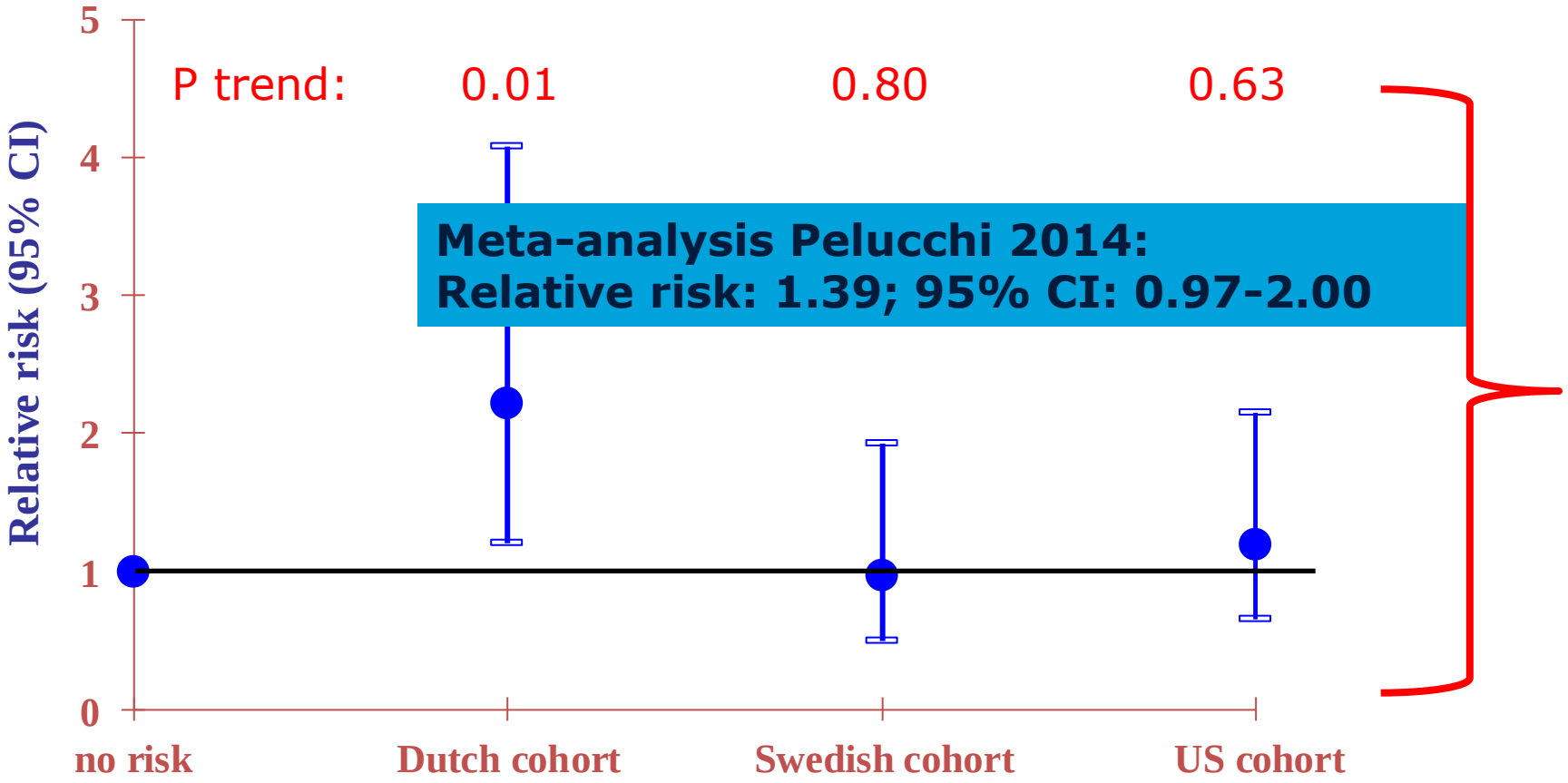
Questions?

Ovarian cancer

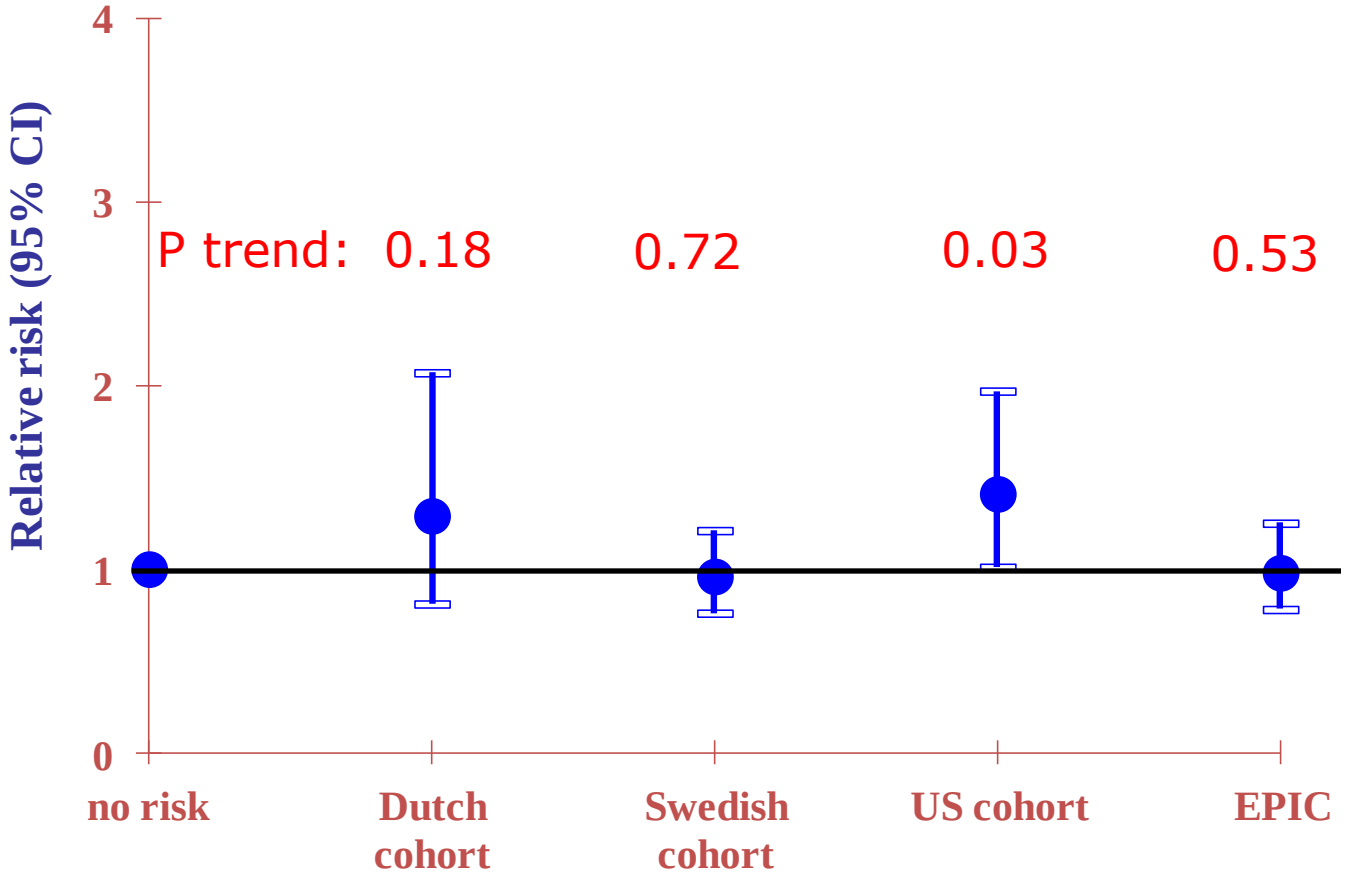
- FFQ
- Highest vs lowest category of AA intake
- Corrected for covariables (confounders)



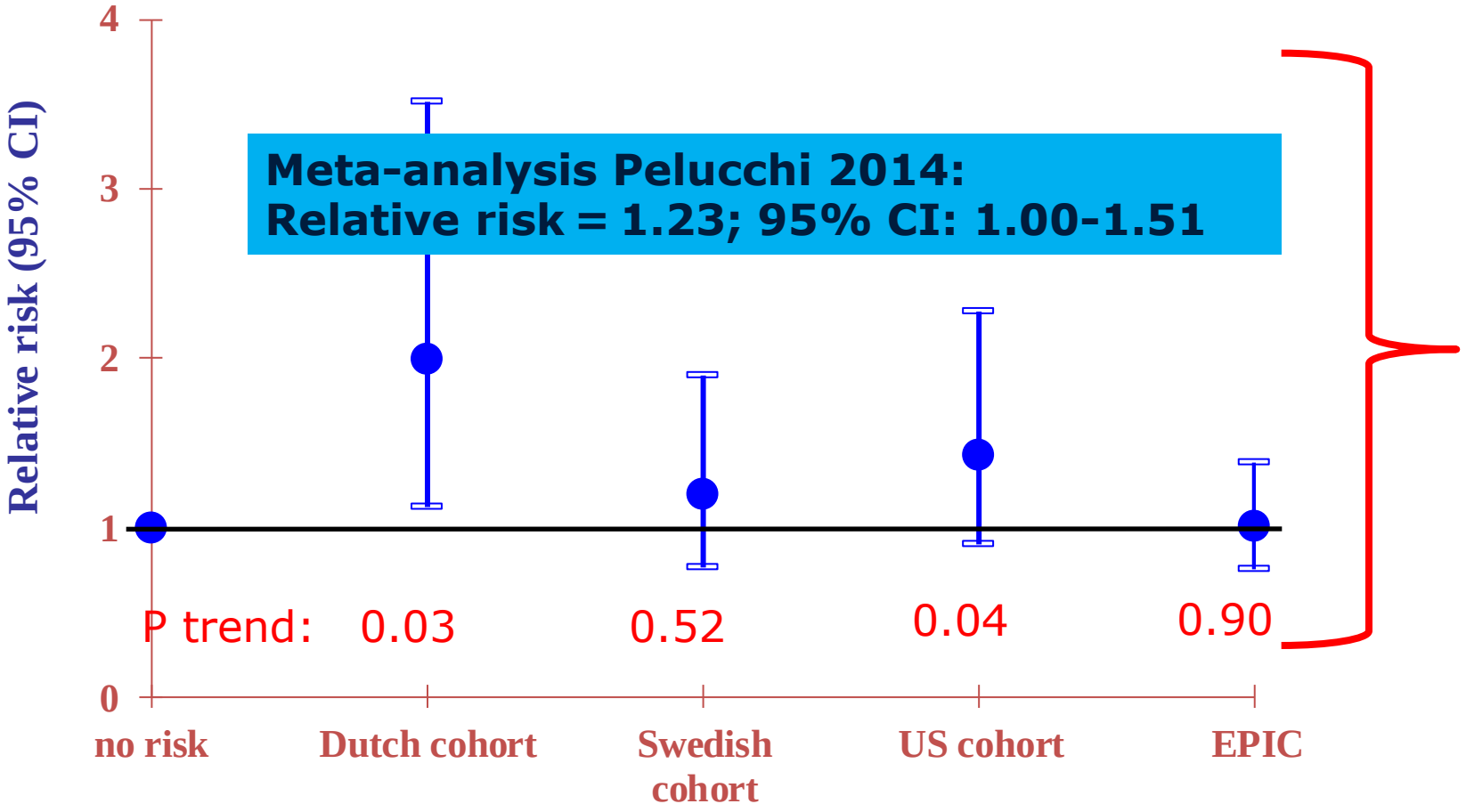
Ovarian cancer, never-smokers



Endometrial cancer



Endometrial cancer, never-smokers



Kidney cancer