EVALUATION DE LA CANCEROGENESE DES MEDICAMENTS – QUOI DE NEUF?

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Overview

- A little bit of History
- Carcinogenesis and Mechanisms
- Present regulations
- Propositions for change
- Retrospective Analysis
- Weight of Evidence Approach
- Conclusions

A little bit of History

- Chimney Sweeps

  First Description of Chemical Carcinogenesis (also as an occupational disease!!)

  Scrotal cancer in chimney sweepers in 1775 in England as described by Percival Pott

A little bit of History

- First demonstration of chemical carcinogenesis in animals
  - Yamagiwa and Ichikawa 1918
  - Rabbit skin tumors related to coal tar administration
- "Standard Chronic Bioassay" for carcinogenicity
  - Started in 1960s
  - Enhanced by National Cancer Institute Program
- National Toxicology Program (NTP)
  - Founded in 1978
  - Significant impact on testing approaches
- ICH Guideline for carcinogenicity testing
  - 1990s

A little bit of History

Carcinogenicity Testing

Carcinogenicity Study Observations

Standardized Carcinogenicity Testing

Carcinogenicity Evaluation Experiments

- Short term assays
- Application of molecular basis of Carcinogenicity
- “Humanized” rodents

Carcinogenesis and mechanisms

- The carcinogenic process involves several distinct events:
  - Alterations in cellular DNA (related to initiation)
  - Cytotoxicity and cell death
  - Mitogenesis
  - Regenerative hyperplasia
  - Immune suppression
  - Hormones
  - Dietary factors
  - Loss of differentiation

  (related to promotion)

- A combination of these processes occurs from hyperplasia to benign neoplasms to malignancy depending on the product (progression).

Present Regulations and Protocols

- Carcinogenicity evaluations are based at present upon the following four ICH guidances
  - ICH S1A – Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals
  - ICH S1B – Testing of Carcinogenicity of Pharmaceuticals
  - ICH S1C(R2) – Dose Selection for Carcinogenicity Studies of Pharmaceuticals
  - ICH S2(R1) – Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
- The first 3 together provide recommendations on which pharmaceuticals warrant carcinogenicity testing, appropriate approaches for evaluating carcinogenicity potential and appropriate dose selection

Present Regulations and Protocols

- These guidances date from the early 1990's and the approaches and protocols have been refined from the NTP and other older programs used to investigate chemical carcinogenesis and genotoxic potential of chemical products including pharmaceuticals
- Two 2-year rodent carcinogenicity studies are performed in the rat and mouse using groups of around 50 to 70 animals per sex with 3 dose levels and a double control group (several hundreds of animals per study)
- The genotoxicity package consists of a minimum of 3 different studies, both in vitro and in vivo to investigate the mutgenic and clastogenic potential of products
- More recently the possibility to use 6 month transgenic mouse models to replace the 2-year mouse carcinogenicity study has been proposed and succesfully applied (essentailly Tg rasH2)

Present Regulations and Protocols

- For the 2 year studies, the main criteria for determination of possible carcinogenicity are :
  - Animal survival across groups using Kaplan-Meyer plots with associated Peto analysis
  - Increases or decreases in frequency of both spontaneous and novel rare tumours with potential tansformation to malignancy across groups
  - Cause of death, whether tumour induced or an incidental finding
  - Onset of tumour formation (accelerated or delayed)

- Histopathological analysis is the « gold standard »

Propositions for Change

- It is now recognized that pharmaceutical carcinogenesis probably occurs through one of four major mecahnisms:

  Genotoxicity
  Hormonal dysregulation
  Immunosuppression
  Chronic toxicity

The idea is that these can be assessed elsewhere in the information we have on a product rather than in a full 2 year bioassay

Propositions for Change

- For several years now, both the Industry and the Regulatory Agencies have become unsatisfied with the present approach, particularly for the 2-year rat study(false positive and negative studies)
- Several initiatives have been undertaken already to perform retrospective analyses of multiple data sets using carcinogenicicity studies from over three decades of experience
- Need for the introduction of a more comprehensive and integrated approach to address the risk of human carcinogenicity of pharmaceuticals
- Clarify and update, without compromising safety, the criteria to decide whether the running of a two-year rodent carcinogenicity study for a given pharmaceutical would add any additional value to this risk assessment
- Proposition to pilot a scheme for the submission of a Carcinogenicity Assessment Document (CAD) to regulatory Authorities incorporating data from this integrated approach to address the overall carcinogenic risk . These CADs will then be compared to results from the 2-year rat study for accuracy of the prediction

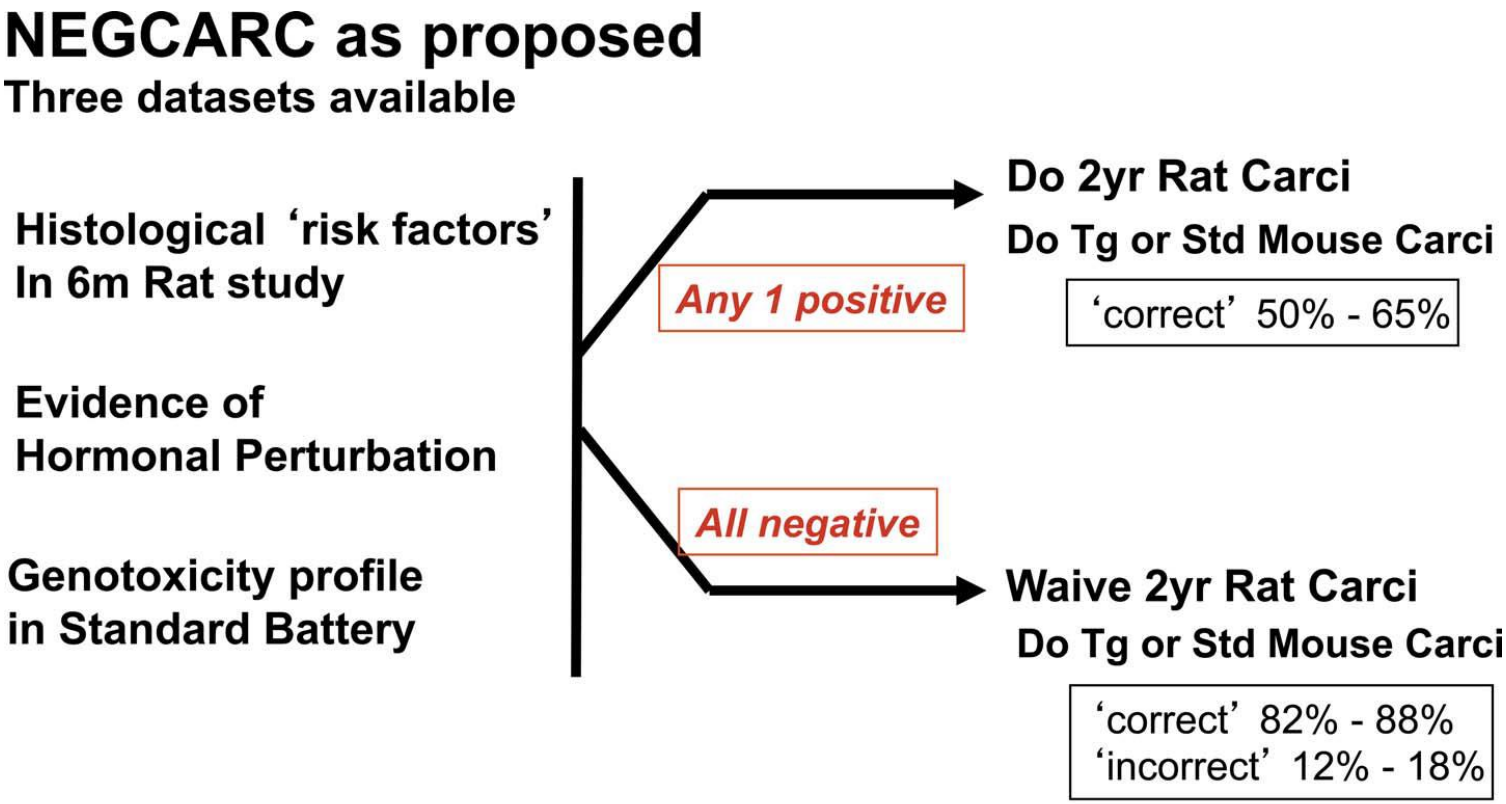
Retrospective Analyses

- Pharma consortium analyzed 182 compounds and showed a good concordance between negative histopathology in the chronic rat study and the 2-year carcinogneicity study, when genetic toxicology, on-target endocrinology and off-target hormonal perturbation effects were included.
- The same effect was applied to 86 IARC Human carcinogens.
- These data were shared with FDA, EMA and MHLW.
- JPMA and FDA conducted independent analyses of additional 60 and 50 paharmaceuticals respectively.
- The decision paradigm of NEG CARC demonstrated potential to eliminate around 40% of 2-year rat testing, BUT an undefined percentage of pharmaceuticals with human relevant cancer risk could escape detection, and the method would be impractical in practice and that non-proliferative histopathological changes of concern may be missed if 2-year testing in rats was eliminated, and only 6 month studies were used.
- It was thus considered a more stratified approach would be more suitable
- Further analyses on other compounds by the FDA and JPMA as well as the relation with the pharmacological activity of compounds have confirmed with more integrated and stratified approach

Definition of NEG CARC

Negative for Endocrine, Genotoxicity, and Chronic Study Associated Histopathologic Risk Factors for Carcinogenicity

Retrospective Analysis



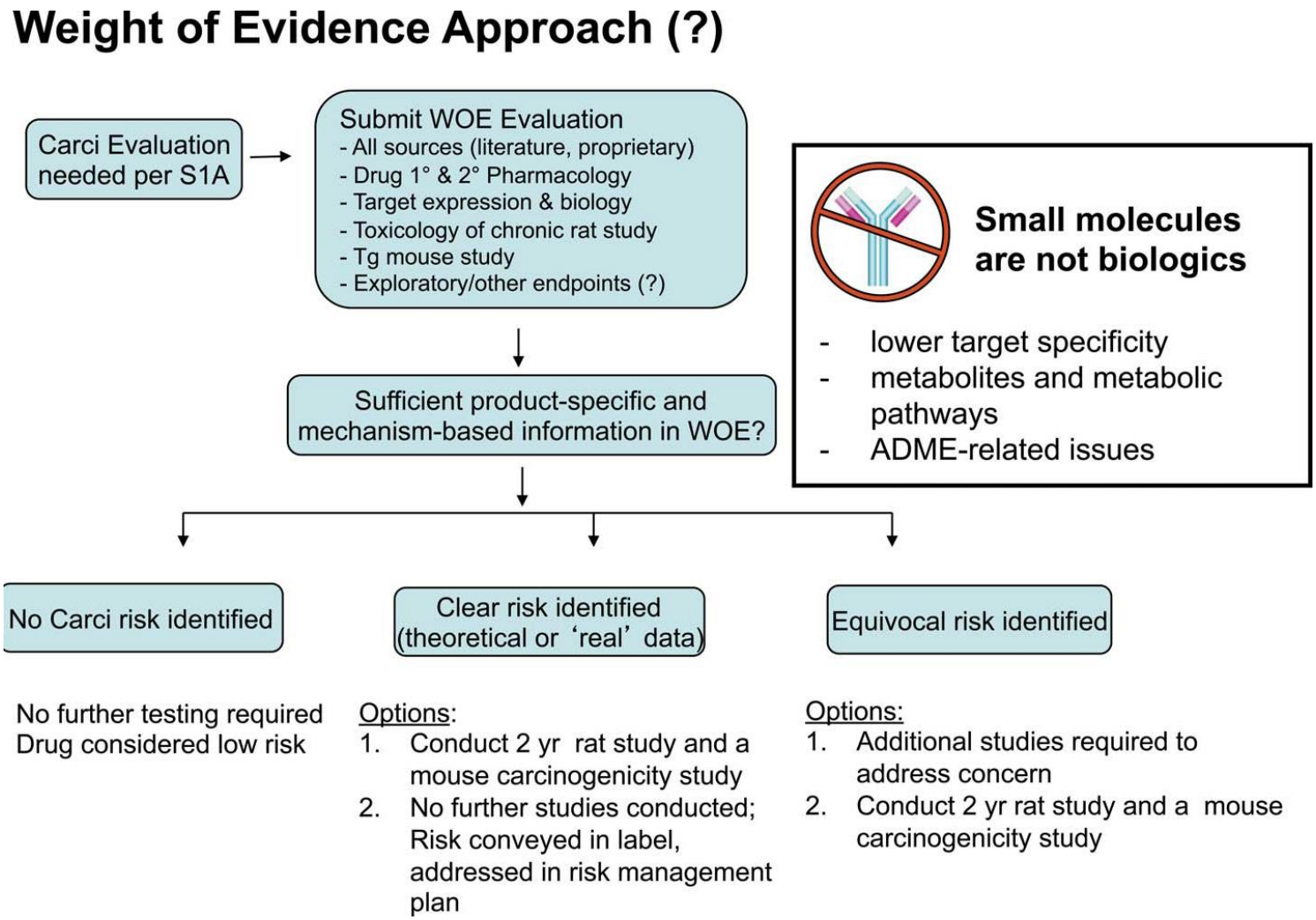
Argued that 18% error rate ('false negatives') negligible because human relevance of 'false negatives' is negligible

From : Morton D et al. (2013) Improving Carcinogenicity Assessment Tox Path **41** 263-270

Weight of Evidence Approach

- Use of the following (non-exhaustive list) factors in formulating outcome and value of conducting 2-year rat carcinogenicity study :
  - Target and pathway realted mechanistic/pharmacologic and secondary pharmacology characteristics
  - Prior experience with other molecules in the drug class
  - Experience with humangenetic polymorphisms in the target or pathway
  - Clinical trial data
  - Genetically engineered rodent models including 6–month rasH2 carcinogenicity studies
  - Animal disease models
  - Unintended pharmacology
  - Hormonal perturbation
  - Targeted tissue genomic biomarker measurements
  - Growth factor signalling pathways(including apoptosis etc)
  - Histopathologic evaluation of repeat dose chronic rat tocicology studies
  - Exposure margins between rat and human
  - Immune suppression
  - Etc……..

Propositions for Change



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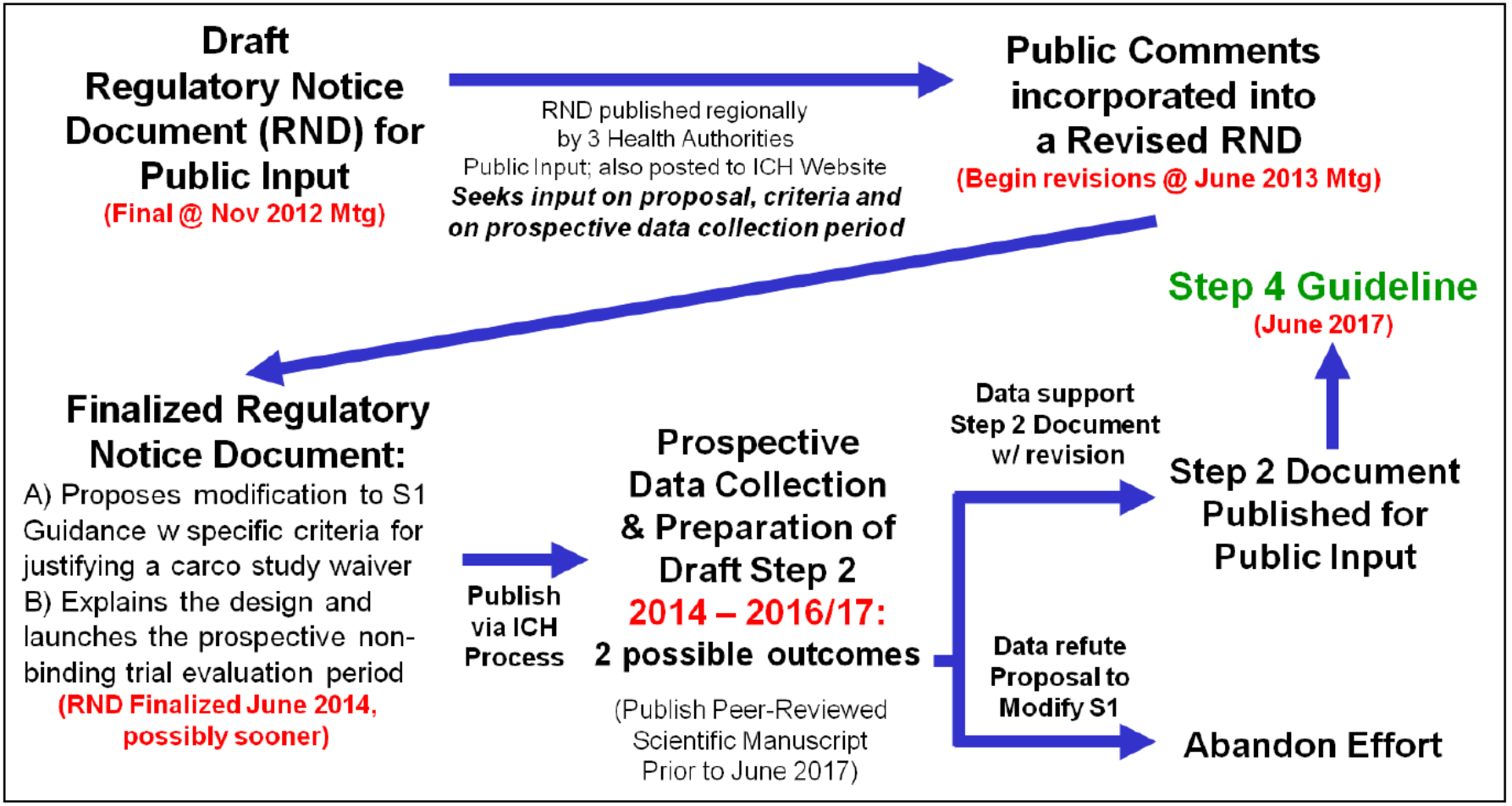
Propositions for Change



From : S1 Rodent Carcinogenicity Studies for Human Pharmaceuticals- Concept Paper
Dated and endorsed by the Steering Committee 14 Nov 2012

Conclusions……so what???

- Real desire to review carcinogenicity risk assessment strategy
- General concensus on how to approach this via ICH with multiple inputs (Industry, Academics, Regulators)
- Fits well with the 3Rs (refine,replace,reduce) for animal use
- Will incorporate new technologies and approaches to better understand the carcinogenic process and reduce potential human risk

Interesting Case to Consider….

Lesions in mesenteric lymph nodes in a 2-year rat study

	Males					Females				
Dose (mg/kg/day)	0	0	5	25	70	0	0	5	25	70
No. Examined	69	69	69	67	70	66	70	68	70	70
Hemangiosarcoma	0	0	0	0	0	0	0	0	0	0
Hemangioma	6	4	2	7	28*	2	2	3	4	6*
Angiomatous hyperplasia	7	9	4	10	22	2	4	11	7	17
Sinusoidal ectasia	45	40	37	45	54	34	51	50	51	48

*** $p < 0.001$ in males, and $p = 0.043$ in females (statistical analysis performed for hemangioma only)**

Thank you!