Disclosures

- Director
- Co-Chair

No direct financial COI

Views expressed my own
Overview

Clinical & Public Health Examples of Evidence integration

- How to integrate
- Human, animal, “mechanistic” evidence - rapid
- Recommendation about use
Goal of systematic reviews

Identify the best quality evidence to support a conclusion:
Exposure/intervention X increases/decreases outcome Y – high certainty
2005/6

World Health Organization had just undergone a review of its guideline methods.

Conclusion: WHO needs to use evidence, synthesized in systematic reviews, for its guidelines.

Avian Influenza threat (H5N1) ~ 200 documented cases of transmission from birds to humans.
WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus
Influenza A Virus

Divided into subtypes on the basis of two proteins on the surface of the virus:

• hemagglutinin (HA) and neuraminidase (NA).
• 18 known HA subtypes and 11 known NA subtypes.
• Many different combinations of HA and NA proteins are possible.
• “H7N2 virus” designates an influenza A virus subtype that has an HA 7 protein and an NA 2 protein.
• “H5N1” virus has an HA 5 protein and an NA 1 protein.
• Different strains (e.g. H1N1 changed in 2009)

CDC website 2019
Avian influenza A (H5N1)

• Powerful virus, spread by migratory birds
• Kills 60%
• Transmits from birds to humans and indications for human to human transmission
• Sporadic human cases, but potential for human pandemic
• Agreement to stockpile antivirals, but no EB guidelines
• Treatment used for regular flu good for H5N1?

• Should oseltamivir be used for treatment of H5N1 in affected adults?
AN INFLUENZA VIRUS

- Antigenic sites
- Hemagglutinin
- Neuraminidase
- M2 ion channel
- Ribonucleoprotein

CDC website 2019
PICO

Population: Avian Influenza (H5N1) patients

Intervention: Oseltamivir

Comparison: No oseltamivir

Outcomes: Mortality, hospitalizations, adverse outcomes, antimicrobial resistance
WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetal Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdani-Panah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbaş, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjidiyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections with H5N1 virus worldwide. Despite international agreement to stockpile antivirals, evidence-based guidelines for their use do not exist. WHO assembled an international multidisciplinary panel to develop rapid advice for the pharmacological management of human H5N1 virus infection in the current pandemic alert period. A transparent

Health in Action

Transparent Development of the WHO Rapid Advice Guidelines

Holger J. Schünemann, Suzanne R. Hill, Meetal Kakad, Gunn E. Vist, Richard Bellamy, Lauren Stockman, Torbjørn Fosen Wisløff, Chris Del Mar, Frederick Hayden, Timothy M. Uyeki, Jeremy Farrar, Yazdan Yazdanpanah, Howard Zucker, John Beigel,
The best evidence – from systematic review(s)

No RCTs in humans infected with H5N1
One case series with 37 patients

- Direct (population)
- Indirect (population)

5 RCTs in seasonal influenza

Animal studies

In vitro
The best evidence

The existing evidence is based on small observational case series of H5N1 patients, results from in vitro and animal model studies of H5N1, or the extrapolation of data from high quality studies conducted to evaluate the treatment and chemoprophylaxis of normal, or “seasonal”, influenza.
Similar enough for treatment to have similar effects?

H5N1  
H1N1 etc

CDC website 2019
Indirect evidence?
Human Animals

P

E

Indirect evidence?

O
Human Animals

E

C

Direct

O
Pick comparator Levels of indirectness
Pick comparator Levels of indirectness

Direct

Human Animals

P

E

C

C₀

O
Pick comparator levels of indirectness

Direct

Human Animals

P

E

C

C₁, C₂, C₃, C₄, C₅

O

no knowledge

Pick comparator levels of indirectness
Pick comparator Levels of indirectness

Human Animals

Direct
no knowledge

Direct (surrogate ?)

Direct
Pick comparator levels of indirectness?

- Direct evidence?
- Indirect evidence?

Human Animals

Mechanism (in vitro) Modelling

Direct

Indirect

Options:
- C
  - C1: no knowledge
  - C2
  - C3
  - C4
  - C5
Human Animals

SRs for all of these elements – diverse evidence?

Direct (surrogate?)

Indirect evidence?

Mechanism (in vitro) Modelling

Direct

Pick comparator Levels of indirectness

C

C1 no knowledge

C2

C3

C4

C5
Direct evidence? No knowledge

Pick comparator Levels of indirectness

C

Mechanism (in vitro) Modelling

SRs for all of these elements – diverse evidence?

Human Animals

Direct (surrogate ?)

Indirect evidence?

Judge indirectness

E

P
Diagram showing the process of evidence integration and conclusion:

1. Specific Question
2. Evidence Streams
   - Human Studies
   - Animal Studies
   - Mechanistic Studies
3. Systematic Review
4. Evidence Integration
5. Conclusion

This diagram illustrates the steps involved in integrating evidence to form a conclusion.
Mechanistic data

Mechanistic data come from a wide variety of studies and are generally not intended to identify a disease phenotype. This source of experimental data includes in vitro and in vivo laboratory studies directed at identifying the cellular, biochemical, and molecular mechanisms that are related to chemicals that produces particular adverse effects.
Indirect evidence?

Direct evidence?

Mechanism (in vitro) Modelling

Direct (surrogate ?)

Indirect evidence?

Judge indirectness

Human Animals

C

P

I

O
SCENARIO: Should oseltamivir be used for treatment of patients hospitalised with avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Hospitalised, clinical and serologically confirmed cases of avian influenza
Information sources:
Clinical trial data: trials for non-H5N1 influenza undertaken in the USA, China, Canada, Europe and Japan under pandemic conditions or seasonal outbreaks.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Avian Influenza H5N1 Evidence</th>
<th>Seasonal Influenza Evidence (may provide indirect evidence of potential benefit in avian influenza)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of studies</td>
<td>Risk without treatment</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.64 (33 to 100%)</td>
<td>0</td>
</tr>
<tr>
<td>Duration of hospitalization (days) 1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Duration of disease (fever) 2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Resistance</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Serious adverse effects²</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Cost of drugs per patient</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Footnotes:
1. In a single trial of healthy elderly participants, there was one death recorded in the placebo arm (n=91) with no deaths occurring in the treatment arm (n=77). No cause of death was given.
2. These data are indirect (i.e. for non-avian influenza) and thus only a proxy measure for what might be expected for avian influenza (H5N1).
3. This is the total number of participants for these 5 trials, confirmed from 3 sources, the ITT population was 1720. The ITTI population was 1404.
4. These data are based on 4 studies and the median time to resolution of symptoms.
5. Major uncertainty about the directness of the evidence, in addition there was significant inconsistency between the results of the studies.
H5N1 was isolated from 2 patients in Viet Nam who died, who had been treated with oseltamivir. Viral isolates had an H274 neuraminidase base substitution which was associated with high level oseltamivir resistance in vitro. H274Y has also been shown to confer oseltamivir resistance in an animal model.
One study has evaluated the effect of oseltamivir on neuraminidase and viral replication using H5N1 isolates from humans. Two additional studies using H5N1 isolated from ducks evaluated the effect of oseltamivir on viral replication (see annex 3). Consistent animal data from three studies in mice indicate that high-dose oseltamivir treatment increased survival in this animal model.

A recent report of 8 cases (6 of these had complete data) described that 3 H5N1 patients who had cleared pharyngeal viral RNA by the end of 5 days treatment with oseltamivir survived. Three patients whose pharyngeal samples remained positive despite therapy died, two of whom had emergence of oseltamivir-resistant variants (de Jong NEJM 2005).

No evidence of resistance reported for H5N1. Viral isolates with the H274 neuraminidase base substitution which confers high level oseltamivir resistance are zanamivir sensitive in vitro.

There are very few studies describing animal and in vitro data about the effects of zanamivir on the H5N1 virus. Zanamivir is active in vitro and in vivo against oseltamivir-resistant H5N1 virus that contains the H274Y mutation (Le 2005).
Similar enough for treatment to have similar effects?

H5N1

H1N1 etc
Judgments

Similar virus: animal and in vitro data, characterization of the virus

- Population: Related, possibly same mechanism of action for neuraminidase inhibitor
- Outcomes: Resistance in animal models = humans

Mechanistic data helped to not dismiss the evidence from non-H5N1 studies

But: rated down for population indirectness because effects may be substantially different
### Amsterdam Oseltamivir versus placebo for treatment of avian influenza (H5N1)

**Should Oseltamivir vs. Placebo be used for treatment of Avian Influenza (H5N1)?**

Oseltamivir compared to Placebo for treatment of Avian Influenza (H5N1)

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of studies</strong></td>
<td><strong>No of patients</strong></td>
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<tr>
<td></td>
<td><strong>Oseltamivir</strong></td>
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**Mortality**

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**Hospitalisation (Hospitalisation from influenza - influenza cases only)**

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**Duration of hospitalisation**

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**Lower respiratory tract infections (Pneumonia - influenza cases only)**

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**Duration of disease (assessed with: Time to alleviation of symptoms/median time to resolution of symptoms - influenza cases only)**

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**Viral shedding (assessed with: Mean nasal titre of excreted virus at 24h)**

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**Outbreak control**

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**Resistance**

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**Serious adverse events (assessed with: Mention of significant or serious adverse effects)**

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**Minor adverse effects (assessed with: number and seriousness of adverse effects)**

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</table>
### Should Oseltamivir vs. Placebo be used for treatment of Avian Influenza (H5N1)?

#### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Absolute Effect</th>
<th>Differences in outcomes</th>
<th>Certainty of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Placebo</td>
<td>With Oseltamivir</td>
<td>More with Placebo</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mortality</td>
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<tr>
<td>Hospitalisation</td>
<td></td>
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<tr>
<td>Duration of hospitalisation</td>
<td></td>
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<tr>
<td>Lower respiratory tract infections (Pneumonia - influenza cases only)</td>
<td>14 per 1000</td>
<td>2 per 1000</td>
<td>12 fewer per 1000 patients</td>
</tr>
<tr>
<td>Duration of disease</td>
<td></td>
<td></td>
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<tr>
<td>CRITERIA</td>
<td>SUMMARY OF JUDGEMENTS</td>
<td>IMPORTANCE FOR DECISION</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------</td>
<td>--------------------------</td>
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</tr>
<tr>
<td>Problem</td>
<td>No</td>
<td>Probably no</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Desirable effects</td>
<td>Trivial</td>
<td>Small</td>
<td>Moderate</td>
</tr>
<tr>
<td>Undesirable effects</td>
<td>Large</td>
<td>Moderate</td>
<td>Small</td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>Very low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Values</td>
<td>Important uncertainty or variability</td>
<td>Possibly important uncertainty or variability</td>
<td>Probably no important uncertainty or variability</td>
</tr>
<tr>
<td>Balance of effects</td>
<td>Favors the comparison</td>
<td>Probably favors the comparison</td>
<td>Does not favor either the intervention or the comparison</td>
</tr>
<tr>
<td>Acceptability</td>
<td>No</td>
<td>Probably no</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Feasibility</td>
<td>No</td>
<td>Probably no</td>
<td>Probably yes</td>
</tr>
</tbody>
</table>
**RECOMMENDATION**

**WE RECOMMEND THE INTERVENTION**

In patients with confirmed or strongly suspected H5N1 infection, we recommend/suggest clinicians (do not) administer oseltamivir treatment as soon as possible (strong/conditional recommendation, high/moderate/low/very low quality evidence).

The recommended dose for seasonal influenza is 75 mg twice daily in adults or the following weight-adjusted doses in children for 5 days (CDC 2006a, CDC 2006b and appropriate FDA label).
- Children 1 year of age or older: weight-adjusted doses
  - 30mg twice daily for ≤ 15 kg
  - 45mg twice daily for >15 to 23 kg
  - 60mg twice daily for >23 to 40kg
  - 75mg twice daily for >40kg

Patients with renal impairment, i.e. a creatinine clearance between 10 and 30 ml/min, who are being considered for oseltamivir treatment require dose reduction. Based on unpublished pharmacokinetic data from the manufacturer, a dose of 75 mg once daily could be used in these patients.
Box 1. Key Steps in the Development of WHO Rapid Advice Guidelines

Decision about the topic and focus of the guidelines January 2006

Decision about group composition and invitation of panel

Formulation of questions and rating the importance of outcomes

Literature search and preparation of evidence profiles February 17, 2006
WHO panel co-chair met with systematic reviewers
Panel chair and WHO panel co-chair corresponded electronically with systematic reviewers

Review of evidence profiles and draft guidelines
Panel chair met with WHO panel co-chair and systematic reviewers

Panel meeting March 28–29, 2006
Information about methods and agreement on procedures at the meeting
Declaration of conflicts of interest
Deliberation regarding the balance of benefits, harms, and costs for each question
Agreement on recommendations, including the strength of recommendations, and research priorities
Plans for updating the guidelines

Agreement on final text of guidelines April 21, 2006
Circulation of draft guidelines
Approval by panel members

Approval/publication by WHO May 19, 2006
Preface

Using GRADE to respond to health questions with different levels of urgency

Kristina A. Thayer a, Holger J. Schünemann b,*

a Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, P.O. Box 12233, Mail Drop K2-02, Research Triangle Park, NC 27709, USA
b Department of Clinical Epidemiology & Biostatistics, Department of Medicine, McMaster University, Health Sciences Centre, Room 2C14, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

Increasing interest exists in applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health evidence. While ideally applied to evidence synthesized in systematic reviews and corresponding summary tables, such as evidence profiles, GRADE’s correct application requires that “the evidence that was assessed and the methods that were used to identify and appraise that evidence should be clearly described.” In this article, we suggest that GRADE could be applied to evidence assembled from narrative reviews, modelled (indirect) evidence, or evidence assembled as part of a rapid response, if the underlying judgments about the certainty in this evidence are based on the relevant GRADE domains and provid
<table>
<thead>
<tr>
<th>Type of response</th>
<th>Ultra-short emergency response: within one or more hours</th>
<th>Urgent response: one to two weeks</th>
<th>Rapid response: one to three months</th>
<th>Routine response: more than 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>West Virginia Elk River spill</td>
<td>Melamine in composite food</td>
<td>Avian influenza</td>
<td>PFOA and birth weight</td>
</tr>
<tr>
<td></td>
<td>Population: community exposed to the chemical spill.</td>
<td>products</td>
<td>Population: people with suspected</td>
<td>Population: women of reproductive</td>
</tr>
<tr>
<td></td>
<td>Intervention/exposure: chemicals in the spill that</td>
<td>from composition food products</td>
<td>avian influenza infection.</td>
<td>age and fetuses (before and/or</td>
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<td>contaminated water supply.</td>
<td>below 0.5 mg/kg body weight per</td>
<td>Intervention/exposure: oseltamivir.</td>
<td>during pregnancy or development).</td>
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<td>Comparison: no chemicals in the spill.</td>
<td>day.</td>
<td>Comparison: no oseltamivir.</td>
<td>Intervention/exposure:</td>
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<tr>
<td></td>
<td>Outcomes: genotoxicity,</td>
<td>Comparison: higher than 0.5</td>
<td>Outcomes: mortality, duration of</td>
<td>perfluorooctanoic acid (PFOA; CAS#</td>
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<td></td>
<td>developmental or reproductive</td>
<td>mg/kg body weight of melamine</td>
<td>hospitalization, incidence of lower</td>
<td>335-67-1) or its salts.</td>
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<td>toxicity, liver toxicity and others.</td>
<td>from composition food.</td>
<td>respiratory tract complications</td>
<td>Comparison: lower levels of PFOA.</td>
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<tr>
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<td>Outcomes: renal insufficiency</td>
<td>(used for this example of the</td>
<td>Outcomes: fetal growth, birth</td>
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<tr>
<td></td>
<td></td>
<td>(assessed with renal clearance),</td>
<td>certainty assessment below),</td>
<td>weight, other measures of fetal or</td>
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<td></td>
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<td>urinary tract calculi, urinary</td>
<td>antiviral drug resistance existing</td>
<td>newborn size.</td>
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<td>tumors (used for this example</td>
<td>before treatment, and serious adverse events.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>of the certainty in the evidence).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of evidence</td>
<td>Available evidence: animal toxicology studies in</td>
<td>Available evidence: animal</td>
<td>Available evidence: five randomized</td>
<td>Available evidence: a systematic</td>
</tr>
<tr>
<td></td>
<td>rodents for two chemicals in the spill (a 28-day</td>
<td>toxicology studies in rat and</td>
<td>trials in patients with seasonal</td>
<td>review of 18 non-randomized</td>
</tr>
<tr>
<td></td>
<td>study and a teratology study) and SAR analyses for</td>
<td>mice with exposures to various</td>
<td>flu (summarized in systematic</td>
<td>(observational) studies (10 were</td>
</tr>
<tr>
<td></td>
<td>other chemicals in the spill with no toxicity data.</td>
<td>levels of melamine via feeding,</td>
<td>reviews), case studies of patients</td>
<td>included in a meta-analysis).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>including a control group.</td>
<td>with avian influenza, <em>in vitro</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>The utilized evidence</td>
<td>and <em>in vivo</em> animal data.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments (note these are not necessarily reflecting judgments in the original scenarios).

Risk of bias
- Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g., randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals
- Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g., randomization, pathologists blinded in their assessments or all animals accounted for). In this case it
- Not serious
- Serious based on some concern of risk of bias in the included studies (in the original report, the authors used an approach to rating certainty that accounted for risk of bias by lowering the certainty from high to
Table 1
Examples of GRADE applied across different time scenarios.

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Ultra-short emergency response: within one or more hours</th>
<th>Urgent response: one to two weeks</th>
<th>Rapid response: one to three months</th>
<th>Routine response: more than 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>West Virginia Elk River spill</td>
<td>Melamine in composite food products</td>
<td>Avian influenza</td>
<td>PFOA and birth weight</td>
</tr>
<tr>
<td></td>
<td>Intervention/exposure: chemicals in the spill that</td>
<td>Intervention/exposure: melamine</td>
<td>avian influenza infection.</td>
<td>age and fetuses (before and/or</td>
</tr>
<tr>
<td></td>
<td>contaminated water supply.</td>
<td>from composition food products</td>
<td>Intervention/exposure: oseltamivir.</td>
<td>during pregnancy or development).</td>
</tr>
<tr>
<td></td>
<td>Comparison: no chemicals in the spill.</td>
<td>below 0.5 mg/kg body weight per</td>
<td>Comparison: no oseltamivir.</td>
<td>Intervention/exposure: perfluoro</td>
</tr>
<tr>
<td></td>
<td>Outcomes: genotoxicity,</td>
<td>day.</td>
<td>Outcomes: mortality, duration of</td>
<td>octanoic acid (PFOA; CAS# 335-67-1)</td>
</tr>
<tr>
<td></td>
<td>developmental or reproductive</td>
<td>Comparison: higher than 0.5 mg/kg body weight of melamine from composition food.</td>
<td>hospitalization, incidence of lower respiratory tract complications</td>
<td>or its salts.</td>
</tr>
<tr>
<td></td>
<td>toxicity, liver toxicity and others.</td>
<td>Outcomes: renal insufficiency</td>
<td>(used for this example of the</td>
<td>Comparison: lower levels of PFOA.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(assessed with renal clearance),</td>
<td>certainty in the evidence.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>urinary tract calculi, urinary</td>
<td>before treatment or adverse events)</td>
<td></td>
</tr>
<tr>
<td>Type of evidence</td>
<td>Available evidence: animal</td>
<td>tumors (used for this example of</td>
<td>Available evidence: animal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>toxicology studies in rodents for two chemicals in the</td>
<td>the certainty in the evidence.</td>
<td>toxicology studies in rat and mice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>spill (a 28-day study and a teratology study) and</td>
<td></td>
<td>with exposures to various levels of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAR analyses for other chemicals in the spill with</td>
<td></td>
<td>melamine via feeding, including a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no toxicology data.</td>
<td></td>
<td>control group. The utilized</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>evidence should be supported by a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>literature search with transparent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>inclusion and exclusion criteria a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(narrative) summary of that evidence.</td>
<td></td>
</tr>
</tbody>
</table>

GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments about the certainty in the evidence.

- **Risk of bias**
  - Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g., randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals
  - Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g., randomization, pathologists blinded in their assessments or all animals accounted for). In this case it

- **Certainty in evidence**
- **Possible summary statements**
Summary

Focused on highest certainty evidence

Used animal evidence and mechanistic evidence to inform judgments about indirectness

- Dismiss or rate down?
- Integrated in indirectness judgment

Rapidly done, recommendation developed
Justification for the recommendation

This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance and costs of treatment. Despite the lack of controlled treatment data for H5N1, this is a strong recommendation, in part, because there is a lack of known effective alternative pharmacological interventions at this time.
GRADE in urgencies

Organizations in environmental health and other areas looking for structured frameworks for evidence synthesis

• “Fit for purpose” – sometimes systematic review not possible to assemble evidence, i.e., need for emergency response

• GRADE’s certainty in the evidence
Preface

Using GRADE to respond to health questions with different levels of urgency

Kristina A. Thayer a, Holger J. Schünemann a,−

a Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, P.O. Box 12233, Mail Drop K2-02, Research Triangle Park, NC 27709, USA

b Department of Clinical Epidemiology & Biostatistics, Department of Medicine, McMaster University, Health Sciences Centre, Room 2C14, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

Urgent response: one to two weeks

Melamine in composite food products
Population: healthy people
Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day.
Comparison: higher than 0.5 mg/kg body weight of melamine from composition food.
Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).
Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.
<table>
<thead>
<tr>
<th>GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments (note these are not necessarily reflecting judgments in the original scenarios).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias</td>
</tr>
<tr>
<td>Imprecision</td>
</tr>
<tr>
<td>Inconsistency</td>
</tr>
<tr>
<td>Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g., randomization, pathologists blinded in their assessments or all animals accounted for). In this case it appears that the animal studies did not report that it was randomized and, thus, may be at risk of bias.</td>
</tr>
<tr>
<td>Type of response</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Indirectness</td>
</tr>
<tr>
<td>Type of response</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Indirectness</td>
</tr>
</tbody>
</table>

**Possible summary statement**

- There is low certainty in the evidence suggesting no association between the exposure and toxicity based on SAR analyses.
- There is very low certainty in the evidence suggesting no association between levels of melamine exposure from composition food products below 0.5 mg/kg body weight per day and urinary tumors.
- There is very low certainty suggesting that oseltamivir reduces hospitalization in patients with avian influenza.
- There is moderate certainty in the evidence suggesting that PFOA is associated with harmful effects on fetal growth.

* Note, this hypothetical summary was derived by the authors of this editorial, not those of the original report.
Today

• GRADE “very” brief background
• When and how to integrate
• Human, animal, “mechanistic” evidence
Anatomy of a guideline

WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetali Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özboy, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjdaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections with H5N1 virus worldwide. Despite international agreement to stockpile antivirals, evidence-based guidelines for their use do not exist. WHO assembled an international multidisciplinary panel to develop rapid advice for the pharmacological management of human H5N1 virus infection in the current pandemic alert period. A transparent

Lancet Infect Dis 2007; 7: 21–31
Italian National Cancer Institute Regina Elena, INFORMA Unit, Department of
A World Health Organization guideline

WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetali Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjialiyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections. Lancet Infect Dis 2007; 7: 21–31
A World Health Organization guideline

Population: Avian Flu/influenza A (H5N1) patients

Intervention: Oseltamivir (or Zanamivir)

Comparison: No pharmacological intervention

Outcomes: Mortality, hospitalizations, resources, adverse outcomes, antimicrobial resistance

Schunemann, Hill et al., The Lancet ID & PLOS Med, 2007
Oseltamivir for Avian Flu

Summary of findings:

No clinical trial of oseltamivir for treatment of H5N1 patients.

4 systematic reviews and health technology assessments (HTA) reporting on 5 studies of oseltamivir in seasonal influenza.

- Hospitalization: OR 0.22 (0.02 – 2.16)
- Pneumonia: OR 0.15 (0.03 - 0.69)

3 published case series.

Many in vitro and animal studies.

No alternative that was more promising at present. No important side effects.

Cost: 40 Euro per treatment course
After over 20 years of increasing confusion, beginning in 2000, GRADE developed a **unifying, transparent and sensible system for grading the certainty of evidence and making decisions**

- WHO, NICE, CADTH, CDC, AHRQ, professional societies, academic institutions since 2000 – over 100 use GRADE
- Evidence synthesis (systematic reviews, HTA) and guidelines
- International & diverse contributors (>600)
- 2008/16 BMJ series; 2011 -? JCE/EHI series – over 40,000 cites
- Various other publications (incl. GRADE Handbook)
- IT applications **GRADEpro** **GDT**

Approved: South Africa, Czech Rep.,
Planned: Japan, Poland, Brazil

GRADE Centers
- McMaster University GRADE Center, Canada
- Lanzhou University GRADE Center, China
- Barcelona GRADE Center, Spain
- Freiburg University GRADE Center, Germany
- American University of Beirut GRADE Center, Lebanon
- Lazio Region ASL Rome GRADE Center, Italy
- Javeriana Bogota GRADE Center, Colombia
- JBI Adelaide GRADE Center, Australia

GRADE Networks
- U.S. GRADE Network, United States
- Dutch GRADE Network, Netherlands
- UK GRADE Network, United Kingdom
Over 100 organisations
GRADE came from epidemiology
Certainty in causation

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill cbe dsc frcp(hon) frs
(Professor Emeritus of Medical Statistics,
University of London)

Certainty in causation

Meeting January 14 1965

President's Address

observed association to a verdict of causation? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. How such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) Strength. First upon my list I would put the strength of the association. To take a very old
Recommendations & the origin of evidence appraisal systems
Effectiveness of intervention

The effectiveness of intervention was graded according to the quality of the evidence obtained, as follows:

I: Evidence obtained from at least one properly randomized controlled trial.

II-1: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-2: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Effectiveness of intervention

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I: Evidence obtained from at least one properly randomized controlled trial.

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III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Classification of recommendations

On the basis of these considerations the task force made a clear recommendation for each condition as to whether it should be specifically considered in a periodic health examination. Recommendations were classified as follows:

A: There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.

B: There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.

C: There is poor evidence regarding the inclusion of the condition in a periodic health examination, and recommendations may be made on other grounds.

D: There is fair evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

E: There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

This report is complemented by a monograph of supporting documents that detail the scientific basis.
GRADE came from epidemiology

Bradford Hill

David Sackett and colleagues
Etiology

PECO

Association vs. Causation
A sensible question

Population: People

Exposures: Ethylene Oxide

Comparison: no, different levels of, exact cut offs of Ethylene Oxide

Outcomes: different types of cancer

PECO
Decisions

Population: People

Intervention: Regulation to ban/reduce to certain level

Comparison: no regulation

Outcomes: cancer, road safety (ethylene glycol), surgical infections

PICO
Confidence in estimates of effect

Schünemann et al. JECH 2010
Confidence in estimates of effect

100% confident →

← starting point?

0% confident →

Schünemann et al. JECH 2010
Confidence in estimates of effect

Bradford Hill Criteria
- Strength
- Consistency
- Temporality
- Biological gradient
- Specificity
- Biological Plausibility
- Coherence
- Experiment
- Analogy

Schünemann et al. JECH 2010
Confidence in estimates of effect

Bradford Hill Criteria
- Strength
- Consistency
- Temporality
- Biological gradient
- Specificity
- Biological Plausibility
- Coherence
- Experiment
- Analogy

Good, but insufficient (publication bias?)

Schünemann et al. JECH 2010
Why did GRADE not use Bradford Hill Characteristics

- Not complete
- Not operationalized
  - Random error
  - Experimental design
  - Consistency
  - Biological plausibility, etc
- Not completely thought through
  - Association
  - Intervention
  - Prognosis
  - Tests, etc
- Not fit for what follows from an exposure assessment – policy & interventions
Confidence in estimates of effect or causality

Schünemann et al. JECH 2010
Confidence in estimates of effect or causality

100% confident → GRADE’s starting point → 0% confident

High
Moderate
Low
Very low

Schünemann et al. JECH 2010
GRADE considers Bradford Hill
Table 1  Bradford Hill criteria of causality and their relation to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for upgrading and downgrading

<table>
<thead>
<tr>
<th>Bradford Hill criteria</th>
<th>Consideration in GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>Strength of association and imprecision in effect estimate</td>
</tr>
<tr>
<td>Consistency</td>
<td>Consistency across studies, i.e., across different situations (different researchers)</td>
</tr>
<tr>
<td>Temporality</td>
<td>Study design, specific study limitations; RCTs fulfil this criterion better than observational studies, properly designed and conducted observational studies</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>Dose–response gradient</td>
</tr>
<tr>
<td>Specificity</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Coherence</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Experiment</td>
<td>Study design, randomisation, properly designed and conducted observational studies</td>
</tr>
<tr>
<td>Analogy</td>
<td>Existing association for critical outcomes will lead to not downgrading the quality, indirectness</td>
</tr>
</tbody>
</table>

Schünemann et al. JECH 2010
Causality considerations

Not everything made sense
50 years later
Bradford Hill – one person
Spitzer, Sackett et al – few people
GRADE – community of more than 600
Certainty of evidence

How confident in the research?

Are the research studies well done? **Risk of bias**

Are the results consistent across studies? **Inconsistency**

How directly do the results relate to our question? **Indirectness**

Is the effect size precise - due to random error? **Imprecision**

Are these all of the studies that have been conducted? **Publication bias**

Is there anything else that makes us particularly certain? **Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation**
Operationalization

Risk of bias?

Are the results consistent across studies? **Inconsistency**
How directly do the results relate to our question? **Indirectness**
Is the effect size precise - due to random error? **Imprecision**
Are these all of the studies that have been conducted? **Pub. Bias**

Is there anything else that makes us particularly certain? **Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation**
1. BIAS DUE TO CONFOUNDING
2. BIAS IN SELECTION OF PARTICIPANTS INTO THE STUDY
3. BIAS IN CLASSIFICATION OF INTERVENTIONS
4. BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS
5. BIAS DUE TO MISSING OUTCOME DATA
6. BIAS IN MEASUREMENT OF THE OUTCOME
7. BIAS IN THE SELECTION OF THE REPORTED RESULT

Risk of bias assessment is mainly distinct from assessments of randomized trials.

Considerations of bias in observational studies are similar to those in randomized studies.
GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias)

GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence

A risk of bias instrument for non-randomized studies of exposures: A users' guide to its application in the context of GRADE

Evaluation of the risk of bias in non-randomized studies of interventions (ROBINS-I) and the ‘target experiment’ concept in studies of exposures: Rationale and preliminary instrument development
Operationalization

GRADE guidelines: 7. Rating the quality of evidence— inconsistency
Operationalization

Are the results consistent across studies? Inconsistency

Can inconsistency be explained? – PECO items, explore
Overlapping confidence intervals
Similarity of the point estimates
I²
Test for heterogeneity

GRADE guidelines: 7. Rating the quality of evidence—inconsistency
Operationalization

Is the effect size precise - due to random error? Imprecision

Are these all of the studies that have been conducted? Pub. Bias

Is there anything else that makes us particularly certain? Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation
Indirectness – evidence integration

How directly do the results relate to the question of interest? Indirectness

RESEARCH ARTICLE

Facilitating healthcare decisions by assessing the certainty in the evidence from preclinical animal studies

Carlijn R. Hooijmans¹, Rob B. M. de Vries¹, Merel Ritskes-Hoitinga¹, Maroeska M. Rovers¹, Mariska M. Leeflang², Joanna IntHout¹, Kimberley E. Wever¹, Lotty Hooft³, Hans de Beer⁴, Ton Kuijpers⁵, Malcolm R. Macleod⁶, Emily S. Sena⁶, Gerben ter Riet⁷, Rebecca L. Morgan⁸,⁹, Kristina A. Thayer¹⁰, Andrew A. Rooney¹⁰, Gordon H. Guyatt⁸,⁹, Holger J. Schünemann⁸,⁹, Miranda W. Langendam²*, on behalf of the GRADE Working Group¹¹
Whatever the question

The population of interest is in humans
Mechanistic data come from a wide variety of studies and are generally not intended to identify a disease phenotype. This source of experimental data includes in vitro and in vivo laboratory studies directed at identifying the cellular, biochemical, and molecular mechanisms that are related to chemicals that produce particular adverse effects.

Another broad class of mechanistic data relates to the toxicokinetics of a chemical (NRC 2014a).
Indirectness is a continuum
Indirectness is a continuum
Animal studies

- Considered a different species
- Typically indirect, but
- First guidance from WHO in which evidence is considered moderate on the basis of a single study in animals
Indirectness affects all domains

<table>
<thead>
<tr>
<th>Domain (original question asked)</th>
<th>Description</th>
<th>Judgment - Is the evidence sufficiently direct?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Intervention: exposure</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Comparator: [comparison]</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Direct comparison</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Outcome: Cancer</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

Final judgment about indirectness across domains:

- No indirectness
- Serious indirectness
- Very serious indirectness

[Table with options for selection: Cancel, Apply]
Indirectness affects all domains

Outcome: Cancer

<table>
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<td>Yes</td>
</tr>
<tr>
<td>Final judgment about indirectness across domains:</td>
<td></td>
<td>No indirectness</td>
</tr>
</tbody>
</table>

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Preface

Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes

Rebecca L. Morgana, Paul Whaleyb, Kristina A. Thayerc, Holger J. Schünemannb,d,e
Indirectness affects all domains

Five paradigmatic approaches and examples for identifying the exposure and comparator in systematic review and decision-making questions.
Indirect evidence?
Indirect evidence?
Pick comparator Levels of indirectness
Pick comparator Levels of indirectness
Pick comparator levels of indirectness

Direct

Mechanism modelling

Human Animals
In vitro/vivo

C
Pick comparator
Levels of indirectness

E

O
no knowledge
Pick comparator levels of indirectness

Direct

Mechanism modelling

Human Animals In vitro/vivo

P

E

C

C_1, no knowledge

C_2

C_3

C_4

C_5

O
Pick comparator Levels of indirectness

C

Direct

Human Animals In vitro/vivo

Direct (surrogate ?)

Mechanism modelling

P

E

O

C

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C_2

C_3

C_4

C_5
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C
C₁, C₂, C₃, C₄, C₅

Human Animals
In vitro/vivo

SRs for all of these elements - diverse evidence?

Direct (surrogate?)

Indirect evidence?

Mechanism modelling

P

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Judge indirectness

O

Direct

no knowledge
Determinants of certainty in a body of evidence: GRADE

A body of evidence starts as: high | ☒ ☒ ☒ ☒ ☒

5 factors that can lower certainty

1. Risk of bias criteria
   - Lack of randomization (observational studies) lowers confidence to low
2. Inconsistency (or heterogeneity)
3. Indirectness (PICO and applicability)
4. Imprecision
5. Publication bias

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Preface

Using GRADE to respond to health questions with different levels of urgency

Kristina A. Thayer a, Holger J. Schünemann b, *

a Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, P.O. Box 12233, Mail Drop 82-02, Research Triangle Park, NC 27709, USA
b Department of Clinical Epidemiology & Biostatistics, Department of Medicine, McMaster University, Health Sciences Centre, Room 2U34, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

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ABSTRACT

Increasing interest exists in applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health evidence. While ideally applied to evidence synthesized in systematic reviews and corresponding summary tables, such as evidence profiles, GRADE’s correct application requires that “the evidence that was assessed and the methods that were used to identify and appraise that evidence should be clearly described.” In this article, we suggest that GRADE could be applied to evidence assembled from narrative reviews, modeled (indirect) evidence, or evidence assembled as part of a rapid response, if the underlying judgments about the certainty in this evidence are based on the relevant GRADE domains and provided transparently. Health questions that require assessing the certainty in a body of evidence to provide trustworthy answers may range from hours, to days or weeks, to a few months to summaries that allow assessing evidence without short-term time pressures. Time frames of emergent, urgent or rapid evidence assessments will often require relying on existing summaries or rapidly compiling the available evidence and making assessments. Even without available full systematic reviews, expressing the certainty in the evidence can provide useful guidance for users of the evidence and those who evaluate certainty in effects. The ratings also help clarifying disagreement between organizations tackling similar questions about the evidence. Using the structured GRADE domains, narrative or other summaries of the evidence can be presented transparently.

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GRADE and Rapid Response

Using GRADE to respond to health questions with different levels of evidence

Kristina A. Thayer, Holger J. Schünemann

ABSTRACT

Increasing interest exists in applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health evidence. While systematic reviews and corresponding summary tables, such as evidence tables, can provide a comprehensive assessment of the evidence, they may also present a challenge to readers who wish to efficiently locate important results. In this article, we suggest strategies to present evidence tables in a more reader-friendly manner, by providing a synthesis of the evidence in a more easily accessible format. This approach can help to improve the accessibility and usability of evidence tables, facilitating better understanding of the evidence and its implications for decision-making.

Table 1: Examples of GRADE applied across different time samples

- **Type of evidence**
  - Available evidence: animal toxicology studies in rats and mice
  - Available evidence: human toxicology studies
  - Available evidence: human toxicology studies in the liver
  - Available evidence: human toxicology studies in the livers of the liver

- **Example**
  - West Virginia flood spill
  - Population: healthy people
  - Environmental exposure: exposure to flood spill
  - Outcome: mortality, incidence of hospitalizations, incidence of lower respiratory tract complications

- **Type of response**
  - Urgent response: one to two weeks
  - Rapid response: one to three months
  - Routine response: more than three months

- **Risk of bias**
  - Bias in outcome assessment: insufficient evidence
  - Bias in outcome assessment: insufficient evidence
  - Bias in outcome assessment: insufficient evidence

- **Sensitivity analysis**
  - Sensitivity analysis: one study included
  - Sensitivity analysis: one study included
  - Sensitivity analysis: one study included
<table>
<thead>
<tr>
<th>Type of response</th>
<th>Ultra-short emergency response: within one or more hours</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>West Virginia Elk River spill</td>
<td>Melamine in composite food</td>
<td>Avian influenza</td>
<td>PFOA and birth weight</td>
</tr>
<tr>
<td></td>
<td>Population: community exposed to the chemical spill</td>
<td>products</td>
<td>Population: people with suspected</td>
<td>Population: women of reproductive</td>
</tr>
<tr>
<td></td>
<td>Intervention/exposure: chemicals in the spill that</td>
<td>from composition food products</td>
<td>avian influenza infection.</td>
<td>age and fetuses (before and/or</td>
</tr>
<tr>
<td></td>
<td>contaminated water supply</td>
<td>below 0.5 mg/kg body weight per</td>
<td>Intervention/exposure: oseltamivir.</td>
<td>during pregnancy or development).</td>
</tr>
<tr>
<td></td>
<td>Comparison: no chemicals in the spill</td>
<td>day.</td>
<td>Comparison: no oseltamivir.</td>
<td>Intervention/exposure:</td>
</tr>
<tr>
<td></td>
<td>Outcomes: genotoxicity, developmental or reproductive</td>
<td>Comparison: higher than 0.5 mg/kg</td>
<td>Outcomes: mortality, duration of</td>
<td>perfluorooctanoic acid (PFOA; CAS#</td>
</tr>
<tr>
<td></td>
<td>toxicity, liver toxicity and others.</td>
<td>body weight of melamine from</td>
<td>hospitalization, incidence of lower</td>
<td>335-67-1) or its salts.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>composition food.</td>
<td>respiratory tract complications</td>
<td>Comparison: lower levels of PFOA.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outcomes: renal insufficiency</td>
<td>(used for this example of the</td>
<td>Outcomes: fetal growth, birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(assessed with renal clearance),</td>
<td>certainty assessment below),</td>
<td>weight, other measures of fetal or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>urinary tract calculi, urinary</td>
<td>antiviral drug resistance existing</td>
<td>newborn size.</td>
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<tr>
<td></td>
<td></td>
<td>tumors (used for this example of</td>
<td>before treatment, and serious</td>
<td></td>
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<td></td>
<td>the certainty in the evidence).</td>
<td>adverse events.</td>
<td></td>
</tr>
<tr>
<td>Type of evidence</td>
<td>Available evidence: animal toxicology studies in rodents</td>
<td>Available evidence: animal</td>
<td>Available evidence: five randomized</td>
<td>Available evidence: a systematic</td>
</tr>
<tr>
<td></td>
<td>for two chemicals in the spill (a 28-day study and a</td>
<td>toxicology studies in rat and mice</td>
<td>trials in patients with seasonal flu</td>
<td>review of 18 non-randomized</td>
</tr>
<tr>
<td></td>
<td>teratology study) and SAR analyses for other chemicals in</td>
<td>with exposures to various levels</td>
<td>(summarized in systematic reviews),</td>
<td>(observational) studies (10 were</td>
</tr>
<tr>
<td></td>
<td>the spill with no toxicity data.</td>
<td>of melamine via feeding, including</td>
<td>case studies of patients with</td>
<td>included in a meta-analysis).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a control group. The utilized</td>
<td>avian influenza, <em>in vitro</em> and *in</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>evidence should be supported by a</td>
<td>vivo* animal data.</td>
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<td></td>
<td></td>
<td>literature search with transparent</td>
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</table>

**GRADE domains to assess certainty in the evidence:** suggested approaches to making judgments or proposed judgments (note these are not necessarily reflecting judgments in the original scenarios).

| Risk of bias | Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g., randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals | Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g., randomization, pathologists blinded in their assessments or all animals accounted for). In this case it | Not serious | Serious based on some concern of risk of bias in the included studies (in the original report, the authors used an approach to rating certainty that accounted for risk of bias by lowering the certainty from high to
### Table 1
Examples of GRADE applied across different time scenarios.

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</tr>
<tr>
<td></td>
<td></td>
<td>Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).</td>
<td>Outcomes: mortality, duration of hospitalization, incidence of lower respiratory tract complications (used for this example of the certainty in the evidence).</td>
<td>Outcomes: mortality, incidence of adverse events (used for this example of the certainty in the evidence).</td>
</tr>
<tr>
<td>Type of evidence</td>
<td>Available evidence: animal toxicology studies in rodents for two chemicals in the spill (a 28-day study and a teratology study) and SAR analyses for other chemicals in the spill with no toxicology data.</td>
<td>Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.</td>
<td>Available evidence: animal toxicology studies in rats (summary of the original scenarios).</td>
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</table>

#### GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments.
- **GRADE domains**
  - risk of bias
  - imprecision
  - indirectness
  - inconsistency
  - publication bias
  - magnitude, etc.
- **Certainty in evidence**
- **Possible summary statements**
GRADE project groups

Feel free to join

- Environmental Health
- Modelling
- Public Health
Distinguish

Association (GRADE for risk factors)

Causality

Interventions
Decisions

Population: People

Intervention: Regulation to ban/reduce to certain level

Comparison: no regulation

Outcomes: cancer, road safety (ethylene glycol), surgical infections

PICO
GRADE Evidence to Decision (EtD) framework

Can help decision makers move from evidence to a recommendation or decision by:

• Informing judgements about the pros and cons of each option
• Considering each important factor that determine a decision (criteria)
• Providing a concise summary of the best available research evidence to inform judgements
• Helping to structure discussion and identify reasons for disagreements
• Making the basis for decisions transparent and adaptable for target audiences:
  • Clinical and public health
  • Policy making
  • Health systems
  • Coverage decisions
Fig. 1 Evidence to Decision (EtD) conceptual map workflow
Thank you

@schunemann_mac