

UNDERSTANDING THE RISK ASSESSMENT PROCESS

Berna Magnuson, PhD

Fellow, Academy of Toxicological Sciences

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The Calorie Control Council



Risk Assessment for All Chemicals


Natural or Synthetic





RISK ASSESSMENT OF FOOD ADDITIVES

- **Evaluated for safety by an independent scientific body before being approved for use in the given market;**
- **International = JECFA**
 - Joint Food Additives Organization/World Health Organization Expert Committee on Food Additives;
- **European = EFSA, the European Food Safety Authority;**
- **United States = FDA, U.S. Food & Drug Administration;**
- **All establish the maximum exposure or ADI (Acceptable Daily Intake) based on hazard assessment to ensure all food additives pose low risk of harm.**



**Hazard
(Potential
to cause
harm)**

Hazard is assessed by toxicology studies.

For additives to be used in food:

- Short- and life-time toxicity studies in many species
- Effects assessed during pregnancy and development

May include human clinical studies.

Objective: using studies with varying doses, determine Level that causes No Observed Adverse Effect over lifetime.

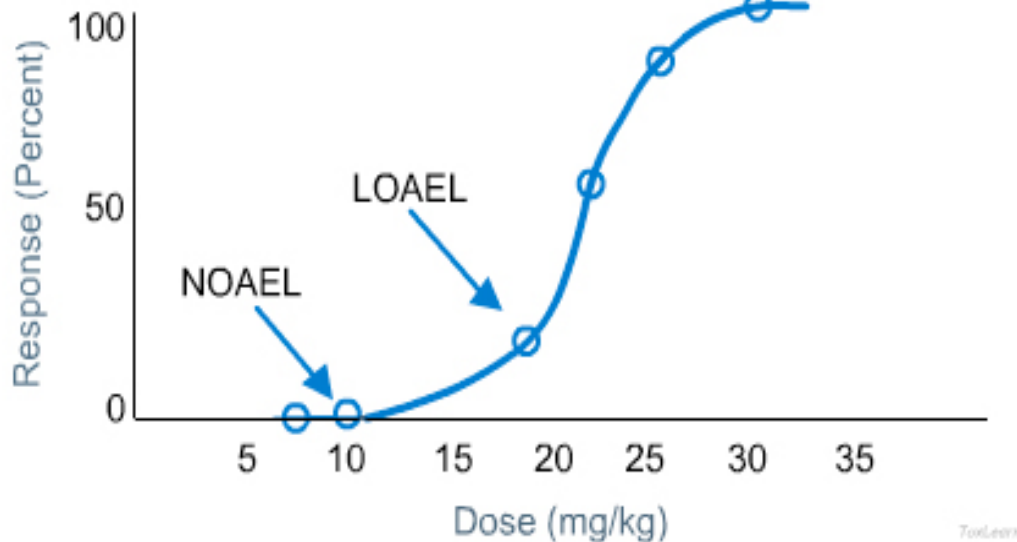
NOAEL is a measure of hazard.

Higher NOAEL = lower toxicity or hazard.

TOXICOLOGY STUDIES

- Does the additive affect the genetic material?
 - Genetic toxicity (mutations);
- Where does additive go when we consume it?
Absorption, metabolism, distribution and excretion
- What adverse effects does the additive cause?
- At what dose do we see adverse effects?
- Any effect on Reproduction?
 - during pregnancy, birth and development;
- Human studies:
 - Only when shown safe in animals
 - Special populations.

NOAEL



-from long-term studies

-use most sensitive species and endpoint

-highest dose that caused no adverse effect

-mg/kg body weight/day

No-Observed Adverse Effect Level (NOAEL)

Lowest Observed Adverse Effect (LOAEL)

Estimate Acceptable Daily Intake (ADI)

Acceptable Daily Intake (ADI) = amount “that can be ingested daily over a lifetime without appreciable health risk” (WHO 1987).

Based on No-Observed Effect Level (NOAEL):

Apply “safety factors” of 100 to account for

- differences between individuals (10 X)
- differences between humans and animals (10 X)

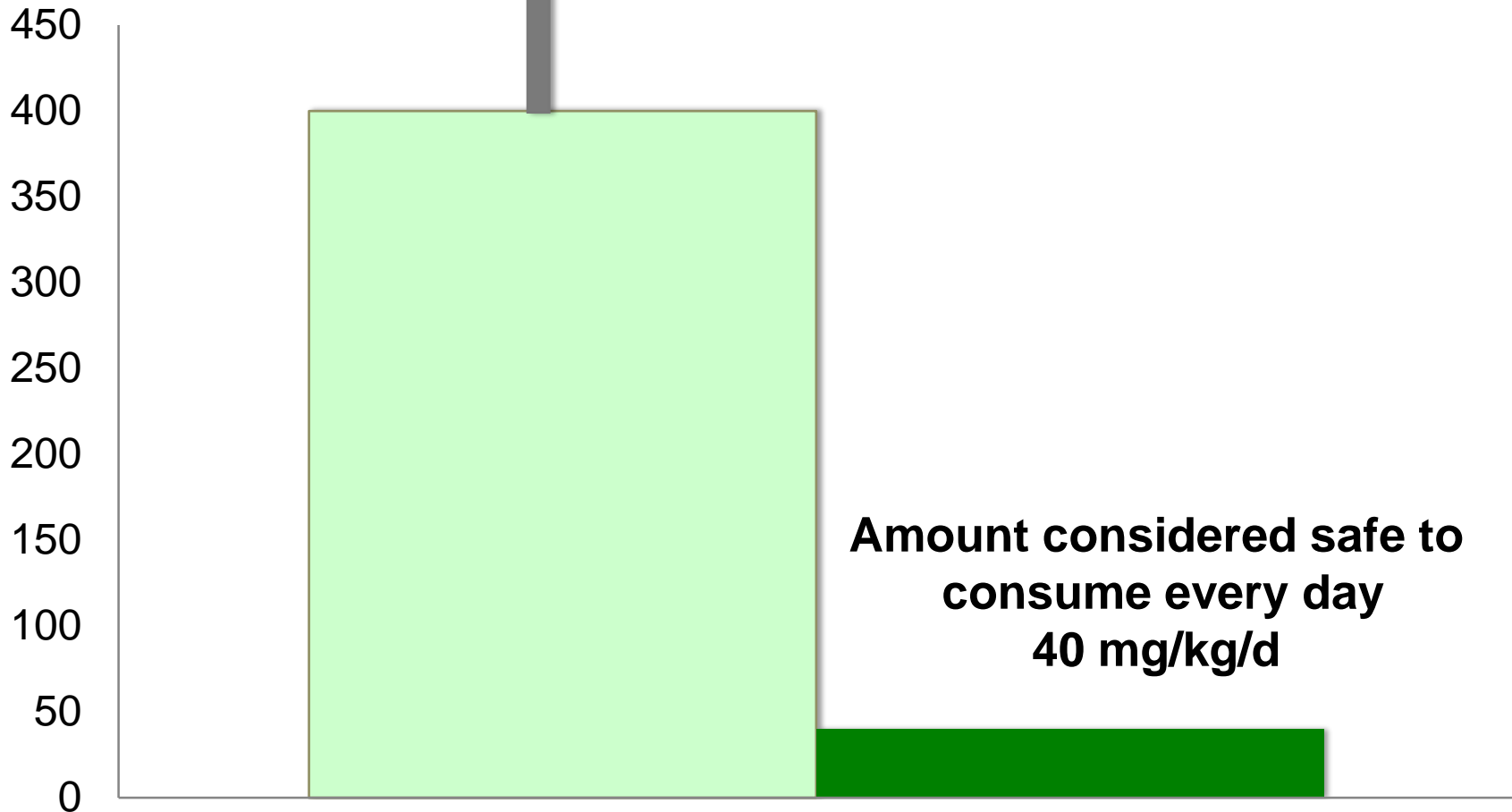
NOAEL/safety factor = ADI (mg/kg/day)

- For example:
 - If NOAEL= 4000 mg/kg/d, ADI = 40 mg/kg/d.
- ADI is very conservative, based on level with no effect when fed to animals for life-time and divided by “safety factor” cushion.

ACCEPTABLE DAILY INTAKE

4000 mg/kg/d

**No observed effect level
in lifetime studies**



ACCEPTABLE DAILY INTAKE

- **Based on the most sensitive critical health outcome in the most sensitive species;**
- **Established to protect the most sensitive sub-population, including pregnant women and children;**
- **ADI is intended to cover exposure of older infants and children, the fetus during pregnancy and the neonatal and young infant periods;**
- **If there is scientific evidence that infants and children are more sensitive to an additive, that evidence must be used in derivation of ADI;**
- **Based on body weight and adjusted for age and size;**
- **International expert report strongly recommended that special ADIs should not be established and that ADI must be safe for all subgroups.**

SAFETY BUILT INTO EXPOSURE ESTIMATE

- **Assume all foods with approved uses have the maximum approved use levels of additive.**
- **Determine intake of foods with approved use by highest consumers.**
- **Includes children and other groups**
- **Ensure no one has estimated intake higher than ADI.**

Disappearance data

- Total production figures; amounts entering the national food chain.

Where and how is food additive used

- Categories listed in food standards legislation and advisory texts (eg Codex General Standard for Food Additives);
- Food industry usage surveys;
- Food labeling surveys.

Use levels

- Maximum permitted levels in food standards legislation
- Industry usage survey levels*
- Analytical data*

* Variability in data – range, 'typical', maximum?

Estimate Range/Distribution of Human Intakes

Individual exposure to additive

OCCURRENCE DATA:

Data on the presence of a food additive in individual foods, including its fate during the processing.

Level of food additive in each food/beverage



FOOD CONSUMPTION:

Data on the consumption patterns of the individual foods containing the food additive.

Amount of each food/beverage consumed



Amount of food additive consumed

Estimate Range/Distribution of Human Intakes

- **Exposure assessment is intended to cover the population, taking into account the variation in food consumption;**
- **Across countries and between various groups of the population, in particular those considered sensitive such as children and the elderly.**
- **Dietary surveys of food consumption used to assess intakes by different groups.**
- **This process is highly conservative as usually the maximum permitted level in food is used together with the maximum amount of food consumed (worst case approach).**

RISK ASSESSMENT PARADIGM

**Identify Hazard
Characterize Dose-Response**

Assess Exposure

**Estimate Acceptable Daily
Intake (ADI)**

**Estimate Range/Distribution
of Human Intakes**

**Characterize Risk
What fraction of the
population, if any, incurs
intakes greater than the ADI?
To what extent do intakes
exceed the ADI?**

Food survey for target
population



SWEETENERS AS AN EXAMPLE

IS THE SWEETENER MUTAGENIC?

- **Usually first toxicology studies to be conducted.**
- **If determined to be genotoxic, no future studies conducted as the sweetener will not be approved**
 - Assess the potential of a sweetener to induce DNA or chromosomal defects (somatic cell) or heritable defects (germ cell).
 - There are many types of tests to determine mutagenicity.
 - The most common battery tests include the Ames test for gene mutations in bacteria, *in vitro* tests and *in vivo* tests.

WHAT HAPPENS TO THE SWEETENER IN THE BODY?

Pharmacokinetics (also called ADME)

- Evaluates the rate and extent of:
 - **Absorption** (how much and where?);
 - **Distribution** (does the sweetener accumulate in any tissues?);
 - **Metabolite formation** (are any toxic?);
 - **Excretion of sweetener** (how quickly? route?).

WHAT HAPPENS TO THE SWEETENER IN THE BODY?

Data from studies allows for an understanding of the following questions:

- Does the animal used in the toxicology testing have similar ADME as humans?
- How much variability is there between individuals?
- Are there any potential susceptible sub-populations?
 - This is used to establish ADI.
- Studies may also provide data on possible mechanisms or modes of toxicity at high concentrations.

DOES THE SWEETENER CAUSE ADVERSE EFFECTS?

All compounds, both natural and man-made, will be toxic at some dose

The goal is to establish a dose that is safe when consumed every day or at the No Observed Effect Level (NOEL)

Extensive testing be conducted in animals, using a minimum of three doses, which are above the expected human exposure levels. Ideally, want:

- Low dose with no observed effect
- High dose that produces mild toxicity
- Mid-range doses to establish dose-response
- For non-toxic, high doses that are studied may be set at an accepted limit dose

Short-term studies conducted to ensure no adverse effects and to establish doses before investing in long-term lifetime studies

DOES THE SWEETENER CAUSE CANCER?

This usually requires a two-year study in rats plus an 18-month study in mice with 20-25 animals/sex per group and at least three dose levels plus a control groups.

Any evidence of dose response in incidence of tumors, time of tumor development, tumors/animal, benign *versus* malignant, and site of tumor development.

Must consider relevance to humans and background incidence.

Studies that do not use the approved methods may not be valid for risk assessment.

DOES THE SWEETENER HAVE ANY EFFECT DURING REPRODUCTION, PREGNANCY AND DEVELOPMENT?

Objective of testing is to determine potential adverse effects on conception, pregnancy, delivery, lactation, neonatal survival and vitality

- Sweetener should be fed to parents before mating, to mother during pregnancy and lactation, then to subsequent generation.

Measurements include:

- Pup weight;
- Number of pregnancies that go to full-term;
- Lactation survival after 21 days;
- Development of offspring
- Necropsy and histopathology of parents with special attention to reproductive organs.

WORST-CASE ASSUMPTIONS FOR ASPARTAME EXPOSURE

Distinction between products **with and without added sugar** was only possible for: *flavoured drinks, confectionery and chewing gums.*

For other food groups, **assumed all products** are sweetened with aspartame at highest level permitted.

- flavoured fermented milk products, edible ices, soups and broths, fruit nectars, desserts, jams and other fruit and vegetable preparations.
- The majority of these products are sweetened with sugar. Low sugar varieties use other heat-stable low-calorie sweeteners.

Result is very conservative exposure estimates, and significant over-estimation of aspartame use.

EXPOSURE ESTIMATE EXAMPLE:

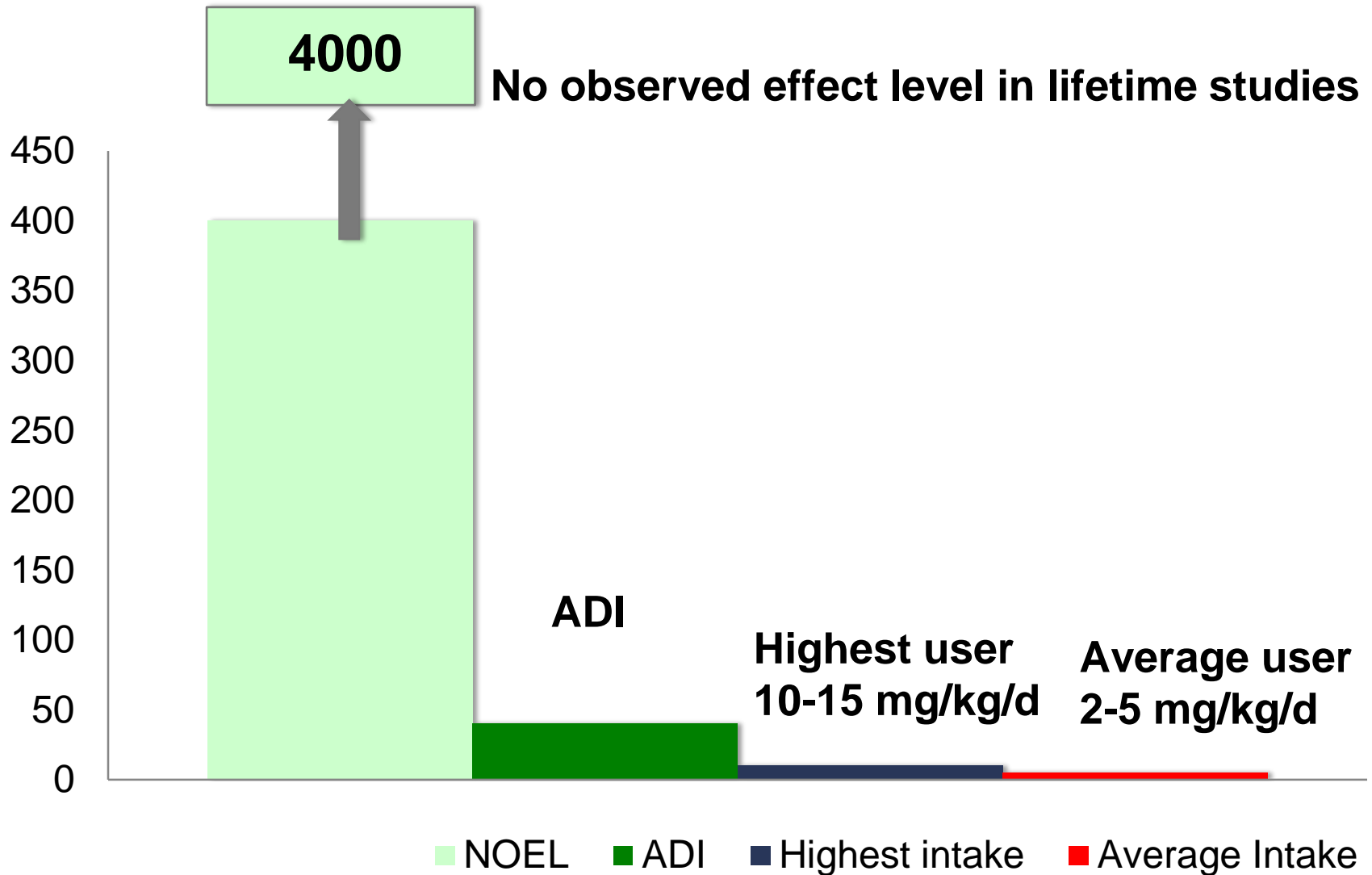
EFSA ESTIMATED ASPARTAME CONSUMPTION IN USERS ONLY

| | Toddler | Children | Adolescent | Adults |
|------------|----------|----------|------------|----------|
| Mean | 1.6-16.3 | 1.8-12.6 | 0.8-4.0 | 0.7-8.5 |
| High level | 7.5-36.0 | 6.3-32.4 | 2.3-13.2 | 2.4-27.5 |

- Reported as mg/kg body weight/day.
- Minimum-maximum across all 26 dietary surveys conducted in 17 different European countries;
- Assumed that all processed foods contained aspartame at maximum permitted level or highest reported use level.
- Compare to ADI of 40 mg/kg/d to ensure no group exceeding

(EFSA 2013)

ACTUAL INTAKES





Intense sweetness = low levels of use



Sugar

$$\div 200-300$$

Sweetness intensity of non-caloric sweetener

WHAT ARE THE CONSEQUENCES OF SWEETENER INTAKES ABOVE ADI?

This question was investigated by an international expert panel (ILSI, 1998)

- Depends on how much above the ADI
- Depends for how often and how long.

There is a often a large difference between the dose that showed no effects (NOAEL) and next higher dose tested that shows adverse effects.

This difference corresponds to an extra safety factor in addition to that normally applied to a NOAEL.

High level of conservatism is built into ADI so that there is low risk of harm from occasional intakes above the ADI in small amounts.

CONCLUSIONS

- There is international harmonization on the approaches and methods used for safety assessment of food additives.
- Toxicity testing requirements for food additives is extensive.
- ADIs are established to protect the entire population and susceptible sub-populations are carefully considered.
- Exposure assessments are very conservative and usually reflect worst case scenarios.
- Use of food additives is not approved until all safety questions have been addressed and estimates of exposures have been determined to be below ADI for all populations.

REFERENCES AND RESOURCES

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Thank you!

Questions?

berna@bernasmagnuson.com