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Environmental Risk Assessments

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Outline

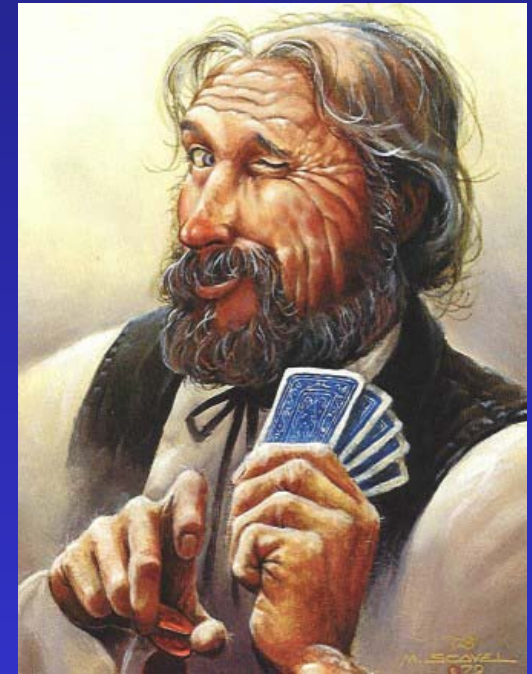
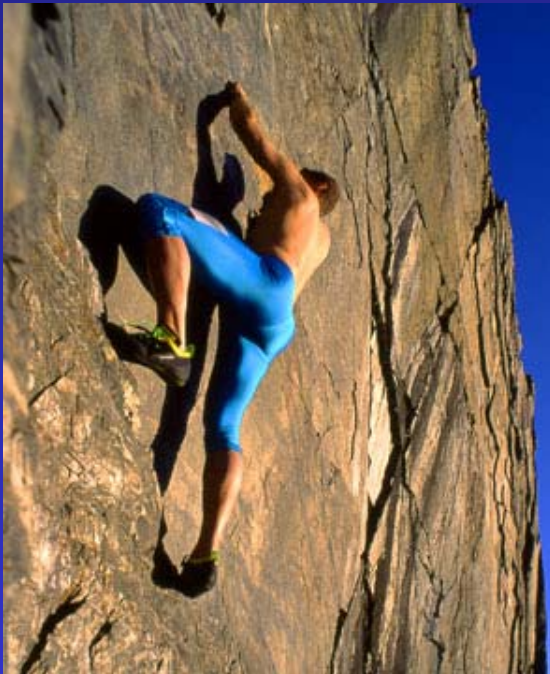
What is Risk?

Environmental Risk

Environmental Assessment

What is Risk?

Risk means different things to different people.



What is Risk?

Quantitative Risk Evaluation

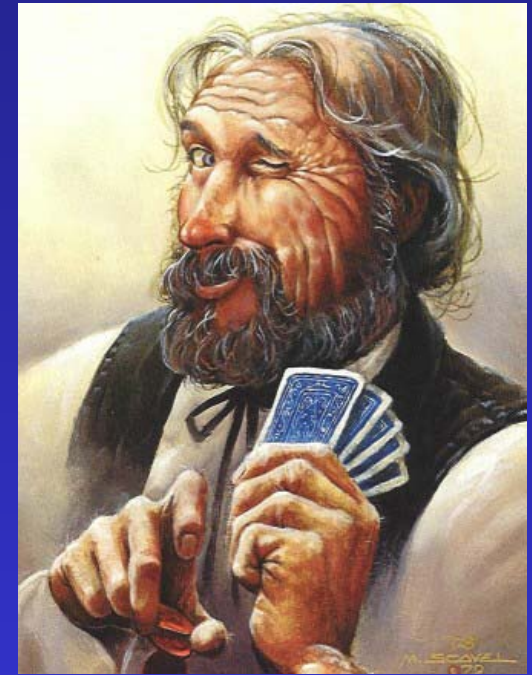
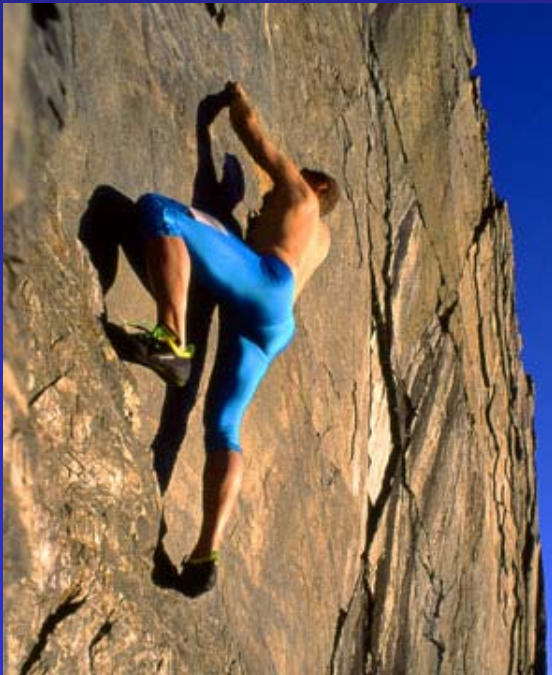
$$\text{Risk} = \text{Hazard} \times \text{Probability}$$

What is a Hazard?

A negative event or outcome.

Some quantitative or qualitative value is needed for hazards because not all hazards are equivalent.

Not all hazards are equal



What is Probability?

A quantitative assessment of the likelihood that the given hazard will occur.

Ranges from ~ 0 to 1.

Environmental Risk

As it relates to plant-made pharmaceuticals:

Risk of spread of viable seed or pollen:

oversight by USDA/APHIS

Risk of environmental contamination by the drug product or structurally-related substances:

oversight by USDA & FDA

Environmental Risk

Acute exposure

Chronic exposure

Risk to humans

Risk to plants

Risk to animals

How does one deal with risk?

Risk Assessment

Risk Management

Risk Mitigation

FDA Guidance

Guidance for Industry

Environmental Assessment of Human
Drug and Biologics Applications

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

July 1998

FDA NEPA Reg 21CFR25.15(a)

Any submission requiring action by the FDA must include either an Environmental Assessment (EA) or a Claim of Categorical Exclusion from the requirement for an EA.

FDA NEPA Reg 21CFR25.15(b)

If an EA is submitted, it is evaluated by the FDA and either an Environmental Impact Statement (EIS) or a Finding of No Significant Impact (FONSI) is filed by the Agency.

Categorical Exclusions - Drugs

21 CFR 25.31

The following actions are generally categorically excluded from needing an EA or an EIS:

- if use of the active moiety does not increase
- if use of the active moiety increases, but the concentration of the substance at the point of entry into the aquatic environment (EIC) will be below 1 part per billion,
- if the substance occurs naturally in the environment and the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment,
- Action on an IND.

... Unless extraordinary circumstances exist

Determining the EIC

The Estimated Introduction Concentration (EIC) =

kg drug produced per year / 365 days

x

10^9 micrograms per kg

x

Liters water per day entering the POTW*

*Publicly-owned treatment works

1.2×10^{11} Liters/day

Source: 1996 Needs Survey, Report to Congress at www.epa.gov/owm

Determining the EIC

1 ppb = 1 microgram per Liter

1ug/Liter x 1.2×10^{11} Liters/day =

120 kg per day =

44,000 kg per year =

~39 million patients at 50 mg per week

Determining the EIC

Assumptions:

- All of the drug product produced is used and enters the publicly-owned treatment works
- Drug product usage occurs throughout the USA in a distribution that is proportional to the population and amount of waste water generated.
- No metabolism occurs.

Refinements

Refinements to the calculations can be made to correct for:

- Metabolism
- Pharmacological activity of metabolites
- Non-proportional distribution of release
- Other factors

Naturally Occurring Substances

A protein or nucleic acid comprised of naturally occurring amino acids or nucleosides, but having a sequence different from that of a naturally occurring substance, will normally qualify as a naturally occurring substance after considering metabolism.

Corn-Produced Biotech Drugs

Antibody against Herpes Simplex Virus

Antibody against Respiratory Syncytial Virus

Gastric Lipase

Human Serum Albumin

Lactoferrin

Collagen

Aprotinin

Hepatitis-B vaccine

Lymphotoxin-B vaccine

Investigational New Drugs

INDs generally involve relatively small amounts of drug and treatment of a limited number of recipients so the environmental exposure is usually low.

INDs will be evaluated on a case-by-case basis to determine if extraordinary circumstances exist.

Extraordinary Circumstances

The determination of extraordinary circumstances can be based on information from:

- The Agency
- The applicant
- Published sources
- Other sources

Extraordinary Circumstances

Extraordinary circumstances include situations where there is a potential for:

- Serious harm to the environment at the expected level of exposure
- Lasting effects on ecological community dynamics
- Adverse effect on an endangered specie or habitat of an endangered specie

The Environmental Assessment

Include:

Physical & chemical characteristics

Locations of emissions

Relevant degradation mechanisms

Results of ecotoxicity testing

Refer to FDA's Environmental Assessment Technical Handbook
(NTIS number PB 87 175345/AS)

Environmental Effects Testing

Tiered approach based on the ratio between the Maximum Expected Environmental Concentration (MEEC) and the median effective concentration (EC_{50}).

Effective Concentration₅₀

Maximum Expected Environmental Concentration

Environmental Effects Testing

The Maximum Expected Environmental Concentration (MEEC) is the concentration that organisms would be exposed to in the environment.

It is derived from the EIC after taking into account any spatial or temporal accumulation or depletion factors, such as dilution, degradation, sorption, or bioaccumulation.

Tiered Environmental Testing

Start off with a Microbial Inhibition Test to determine if the drug has the potential to inhibit microorganisms and thereby interfere with waste treatment processes.

Tiered Environmental Testing

If the drug is rapidly inactivated or degraded under environmental conditions, then it is generally not necessary to institute further testing.

For example:

Hydrolysis $T_{1/2}$ < 24 hours

Aerobic biodegradation $T_{1/2}$ < 8 hours

Soil biodegradation $T_{1/2}$ < 5 days

Tiered Environmental Testing

Assessment Factor =

$$EC_{50}$$

maximum expected environmental concentration

TEST TIER	FACTOR
1	<1000
2	<100
3	<10

Tiered Environmental Testing

Tier 1 Testing: **Acute** ecotoxicity testing should be performed on a minimum of one suitable test organism.

If

EC_{50}

maximum expected environmental concentration

is greater than 1000 and no observed effect at MEEC, then no further testing is needed.

Tier 2 Environmental Test

Acute ecotoxicity testing should be performed on the minimum base set of aquatic and/or terrestrial organisms.

If

EC_{50}

maximum expected environmental concentration

is greater than 100 and no observed effect at MEEC, then no further testing is needed.

Tier 2 Environmental Test

The aquatic base set usually consists of

- (1) a fish acute toxicity test,
- (2) an aquatic invertebrate acute toxicity test, and
- (3) an algal species bioassay.

Tier 2 Environmental Test

The terrestrial base set usually consists of

- (1) plant early growth tests,
- (2) earthworm toxicity tests, and
- (3) soil microbial toxicity tests.

Tier 3 Environmental Test

Tier 3 Testing:

Chronic toxicity testing should be considered

- if the compound has the potential to bioaccumulate or bioconcentrate,
- if indicated based on Tier 1 and/or Tier 2 testing, or
- if there are other indications that the compound undergoes biotransformation to more toxic compounds.

Tier 3 Environmental Test

Chronic ecotoxicity testing should be performed on the base set of aquatic and/or terrestrial organisms.

If

EC_{50}

maximum expected environmental concentration

is greater than 10 and no observed effect at MEEC, then no further testing is needed.

Tier 3 Environmental Test

If ratio is <10 or effects are observed at the MEEC, then you should consult with FDA regarding next steps.

Summary

Consider the physical & chemical characteristics

Determine degradation paths & kinetics

Calculate the EIC and MEEC

Assess categorical exclusion criteria

Are there extraordinary circumstances?

Initiate tiered ecotoxicity testing scheme

Consult the Agency as needed