

Modeling of uncertainty associated with dose–response curves as applied for probabilistic risk assessment in laser safety

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ABSTRACT

In laser safety, dose-response curves describe the probability for ocular injury as a function of ocular energy, and are often used to quantify the risk for ocular injury given a certain level of exposure to laser radiation. In principal, a dose-response curve describes the biological variation of the individual thresholds in a population. In laser safety, a log-normal cumulative distribution is generally assumed for the dose-response curve, for instance when Probit analysis is performed. The log-normal distribution is defined by two parameters, the median, called ED50, and the slope. When animal experiments are performed to obtain dose-response curves for laser induced injury, experimental uncertainty such as focussing errors as well as variability within the group of experimental animals, such as inter-individual variability of absorption of the ocular media, can influence the shape of the dose-response curve.

We present simulations of uncertainties and variabilities that show that the log-normal dose-response curve as obtained in a animal experiments can grossly overestimate the probability for ocular damage for small doses. It is argued that the intrinsic slope for an individual's dose-response curve is rather steep, even for retinal injury, however, the dose-response curve for a group or population can be broader when there is inter-individual variability of parameters which influence the threshold. The quantitative results of the simulation of the grouping of individual dose-response curves can serve as basis to correct potentially biased dose-response curves as well as to characterize the uncertainty associated with the ED50 and the slope of the dose-response curve. A probabilistic risk analysis model, which accounts for these uncertainties by using Monte-Carlo simulation, was developed for retinal laser injuries from pulsed lasers with wavelengths from 200 nm to 20 μm , and the interpretation of the results are discussed on the basis of example calculations.

Keywords: laser safety, probabilistic risk analysis, ocular injury, uncertainty, variability, dose-response curve, Probit analysis, Monte-Carlo simulation

1. INTRODUCTION

The concept of the dose-response curve is widely used in toxicology and health physics. In laser safety, dose-response curves describe the probability of observing a skin or an ocular lesion of a given nature (the response) as a function of laser exposure or energy (the dose). As such, dose-response curves are the basis of both the definition of laser thresholds (exposure limits) as well as of probabilistic risk assessment studies. Aspects of the dose-response curves which are pertinent to the definition of exposure limits are discussed on a phenomenological and biophysical basis in another paper presented at this conference¹; in this paper we present a quantitative mathematical concept to model uncertainties associated with the dose-response curve with special emphasis towards application for probabilistic risk assessment (PRA).

1.1 Point estimate vs. probability distribution

In risk analysis, parameters such as the exposure dose or the shape parameters of a probability distribution can be described in two ways. The possibility of a range of values for the parameter may be expressed as a probability distribution, for example a normal distribution with a mean of 0.8 μJ and a standard deviation of 0.1 μJ , which means the most likely value of exposure is 0.8 μJ , but there can also be higher or lower values. Alternatively, if the value of the parameter is well known and there is negligible spread of the parameter or for a simplistic risk analysis, a point value estimate might be used, for instance a dose value of 1 μJ . To the knowledge of the authors, previous PRA models for laser exposure only considered point estimates for the dose-response curve and for the ocular exposure level. Our analysis shows that there can

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be substantial uncertainty associated with the dose-response curve, which can be partially corrected, but the remaining uncertainty needs to be modeled for a complete PRA characterization. An ocular damage model was developed for exposure to pulsed laser radiation, which models the uncertainty of the dose-response curve by the Monte-Carlo technique.

1.2 Uncertainty and variability

It is helpful for discussion, and also for the completeness of risk models, to note that the spread of possible values of a parameter can be either due to lack of knowledge of the true value, termed uncertainty, or due to (biological) variability². Uncertainty is a description of the imperfection of knowledge about the true single value of a parameter and can be reduced by additional information gathering, better measurements, or analysis. In contrast, variability describes the spread of the parameter which is inherent in the system or population and which cannot be reduced by measurement. For instance, the body weight at birth of a given population can be well described by a normal distribution, and the mean and standard deviation of the distribution, i.e. the shape of the distribution, is well known for countries where measurements are performed on a standardized basis. In a given population, the response to toxic agents (for instance if the sensitivity is directly related to body weight) will show variability, as some individuals will be more sensitive to a given dose than others. Variability can also arise for the exposure parameter of the exposed population, because some individuals will be exposed to a higher dose than others due to variation in the environment or the behavior of the individual. It is typical of variability that it cannot be decreased in extent by additional measurements, but it may be decreased by reducing the population under consideration: for instance, if for one country, babies are generally bigger than for another, the distribution for both countries together will be broader, i.e. there will be a larger spread, than for each of them separately. In the extreme, when the population is reduced to a single individual, the variability distribution of the population for a variable collapses to the value applicable for the individual under consideration. For the case that a risk model does not contain variability, every individual in the population faces an identical risk.

Whilst considering variability and uncertainty, it is interesting to note how they might interact in a specific situation. For example, there may be uncertainty about the amount of variability within a given population. For instance, in developed countries, there are good statistics regarding the weight at birth and the corresponding distribution is well known: however, if measurements of birth weights are not performed on a regular basis, or are performed with poor scales, then there is some uncertainty associated with the actual true shape of the distribution describing the variability in the population. A PRA model, where the uncertainty and variability are modeled separately, is termed second order³.

In the field of risk analysis, there is some variation in the terminology, as often the nature of the spread of a frequency distribution of a parameter is not further considered and the general term “uncertainty” is used. Using “uncertainty” as the overall term, authors in the field of engineering PRA^{4,5} sometimes distinguish between epistemic uncertainty (also called the state of knowledge uncertainty), which is referred to as uncertainty elsewhere and in this paper, and aleatory uncertainty, (also referred to as random or stochastic uncertainty, for instance of the time to failure), which could be compared to variability in the field of environmental health PRA. In some environmental protection studies⁶, variability is termed uncertainty Type A, and uncertainty as used here is termed uncertainty Type B.

Previous PRA models for laser exposure have only considered the variability as represented by a dose-response curve⁷. Here, we describe a second order PRA model for laser exposure, which accounts for the uncertainty of the dose-response curve.

1.3 Dose-response curve

A dose-response curve describes the variability of the sensitivity of a given population to a hazardous agent or “agonist”. Here “population” has to be understood in a rather broad mathematical sense, and can mean a number of retinal exposure sites within an eye, a number of animals for an experiment, or also potentially exposed humans. In laser safety, the response is of “yes” or “no” type, i.e. “lesion” or “no-lesion”. Such a type of response is also called a quantal response, in contrast to a graded response, where an increase in the dose produces a gradual change of the observed phenomena, such as degrees of intoxication following alcohol consumption.

Theoretically, in a given individual when a given tissue site is exposed at a given time, for quantal response there will be a certain sharp threshold dose: below the threshold dose, no response is observed, while if the exposure is above the threshold dose, a response is observed^{**}. Such a situation can be depicted by a step-shaped dose response curve as shown in figure 1.

^{**} It is noted that for a complete information, it is important to specify the nature of response, such as a minimal visible lesion, and also the method of observation, such as ophthalmoscopically, with electron microscope, or other techniques, as discussed further in Reference 1.

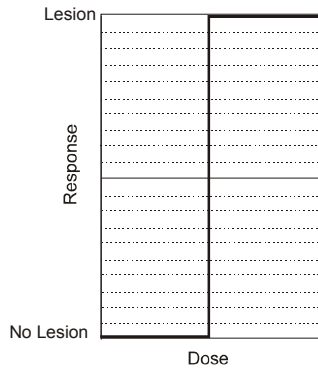


Figure 1. Theoretical dose-response curve without variation. Below a certain threshold dose, no lesion is observed, while above that threshold, exposure always results in a response.

However, it is not possible to determine such a threshold for a single exposure site of a tissue, as a number of exposures are needed to bracket the threshold. and any given point on the retina can only be exposed once, as an exposure damages or potentially changes the properties of the site. Consequently, in laser threshold studies, exposures are performed on a number of different locations on the tissue and also for a number of individuals. Different sites and different individuals will exhibit different thresholds (for instance due to varying retinal absorption, see discussion in Sliney et al. these proceedings¹) and for a given exposure dose, those sites and individuals with a lower threshold dose than the exposure dose will develop a lesion. When the response axis is defined as the relative frequency (percentage) of observed responses from a given total number of exposures with a given dose, then a dose-response curve results, as schematically shown in figure 2.

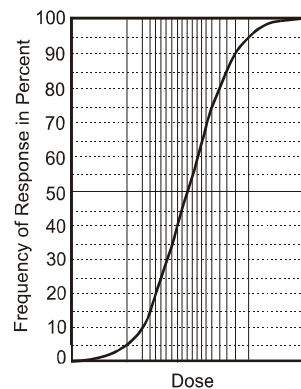


Figure 2. Due to different thresholds of different sites or individuals, for a given exposure dose, only a certain percentage of the exposed population will show a response, and a dose-response curve results.

In figure 2, each vertical line can be conceptualized as an individual sharp threshold step-curve (compare figure 1). The lines are plotted as equidistant frequency, i.e. the intersection with the frequency levels is constant (5 %). Such lines can be also help for graphically determining the shape of the dose-response curve, for instance when two curves from two different “populations” are combined. This is done by counting how many threshold lines lie on the left of any given dose point and dividing by the total number of lines, in this case 20, when the frequency of exposures which will show a response is obtained.

In a mathematical sense, the dose-response curve as shown in figure 2 is a *cumulative* distribution function: when a number of exposures are performed with a given dose, all tissue sites which have a threshold equal to *or smaller than* the exposure dose will show a response. Such a distribution will generally have a sigmoid shape, but it will not be symmetrical, it will be skewed, raising less steeply at the higher dose region because there will always be some tissue samples or individuals, that have a high resistance to damage. An example of a dose-response curve from a laser threshold study is shown in figure 3 with a linear and logarithmic ocular energy scale. As is generally the case for quantal response data⁸, if the abscissa of the frequency distribution is plotted on a logarithmic scale, the data can be fitted well with a cumulative normal (Gaussian) distribution function and all the usual statistical calculations are available. A distribution which is normal when the abscissa is on a logarithmic scale is known as a log-normal frequency distribution.

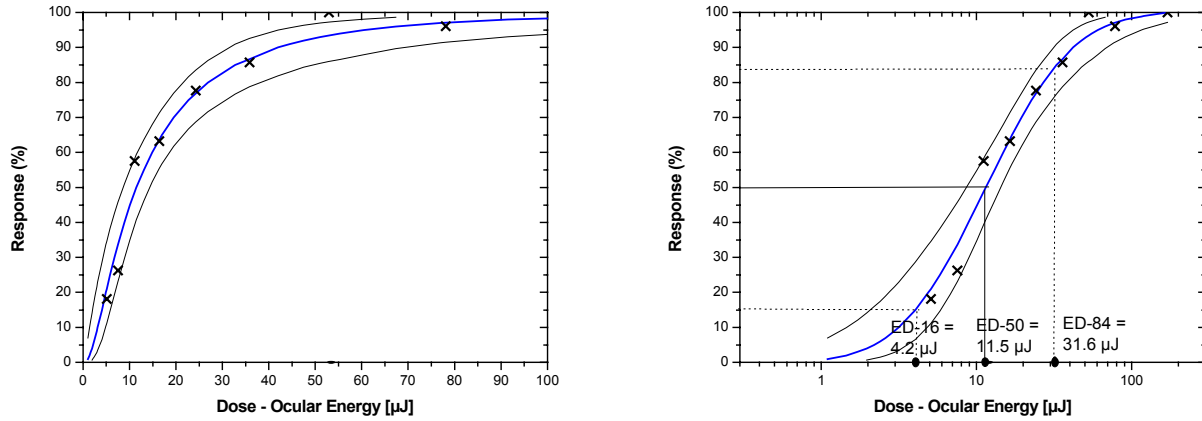


Figure 3. Dose-response curves as obtained from 191 exposures of rhesus monkey retinas to 850 nm, 180 ns laser radiation (private communication J. Lund). The data points (x) are derived by binning of the experimental data into energy intervals and by plotting the resulting relative frequency data for the response between 0 and 1. For instance, if 12 exposures were to fall in a given energy interval or bin, of which 4 showed a response, the relative frequency for response for this bin is 0.33. The lines are the result of a regression with 95 % confidence intervals, where a log-normal cumulative distribution is assumed (probit analysis, see section 1.5)

The log-normal distribution of the response can also be understood on the basis of the central limit theorem of statistics: the variability of a phenomenon or variable is described by a normal distribution, when it arises from many small independent effects in an *additive* way. Since addition of logarithms is equivalent to multiplication of the arguments, a log-normal distribution arises for a variable whenever this variable depends on other small effects in a *multiplicative* way. Consequently, body size and weight are typical examples of normal distributions, as the total observed parameter depends on weight and length of many small portions of the body in an additive way. A typical example of a variable which is described well by a log-normal distribution is the volume of recoverable oil reserves within a field, where the volume is a function of reserve area, thickness, porosity, oil/gas ratio and others³. For the example of exposure to laser radiation, the multiplicative dependency of the effect of the radiation producing a lesion could depend on: the transmissivity of the tissue in front of the site under consideration (total transmissivity is multiplicative regarding different kind of tissues, such as cornea, aqueous, lens, vitreous for exposure of the retina), the absorption depth of the tissue under consideration, and the exposure cross-section.

1.4 Log-normal distribution

The formula for the cumulative log-normal distribution is given by

$$P(OE) = \frac{1}{\ln(S) \cdot \sqrt{2\pi}} \cdot \int_0^{OE} \frac{1}{x} \cdot \exp\left[-\frac{(\ln(x) - \ln(ED50))^2}{2 \cdot \ln(S)^2}\right] dx = 0.5 + 0.5 \cdot \operatorname{erf}\left(\frac{\ln(OE) - \ln(ED50)}{\sqrt{2} \cdot \ln(S)}\right) \quad (1)$$

where OE is the ocular energy (dose), *erf* is the error function, which is tabulated for instance in Reference 9, and is also incorporated in many modern mathematical software packages. ED50 is the median dose, i.e., the dose at which 50 % of the exposures result in a response (a detectable lesion), and is referred to as the “effective dose 50 %,” or simply, the “ED50”. Correspondingly, the dose at which 16 % and 84 % of the exposures result in detected lesions are referred to as ED16 and ED84 respectively. S is the slope, defined as

$$S = \frac{ED84 - ED50}{ED50} = \frac{ED50 - ED16}{ED50} \quad (2)$$

A sharp threshold, as pictured in figure 1, would correspond to a slope S of 1, and the dose response curve in figure 3 has a rather shallow slope S of 2.75. The logarithm of the ED84 and ED16 points represent one-standard deviation in the normal distribution from the logarithm of the median dose. The slope S as defined above can therefore be interpreted as a multiplicative standard deviation¹⁰: instead of “plus/minus” standard deviation as for a normal distribution, the multiplicative standard deviation has to be thought of in terms of “times/divide”. For instance, a slope of S = 2 with an ED50 of 10 μJ would mean that 68 % of the log-normal density distribution is within a range of $10 \times 2 = 20 \mu\text{J}$ and $10/2 = 5 \mu\text{J}$.

1.5 Probit analysis

Today, with modern computers, statistical curve fitting is not a problem, but when toxicology was less developed, a way was sought to allow easy curve fitting with just a ruler and pencil. To simplify the fit of a cumulative log-normal frequency distribution to the data, the data are transformed by turning the cumulative percentage into a probit scale¹¹, which, as figure 4 shows for the example of the data on which figure 3 is based, yields a straight line when the dose is given in logarithmic scale. Thus by transforming the percentage to probits and fitting a best by-eye fit straight line, reliable estimates of ED50 and the slope could be determined. Graphs with these two transformations, logarithmic on the abscissa (dose) and probit on the ordinate (probability for response), are often referred to as „probit plots“.

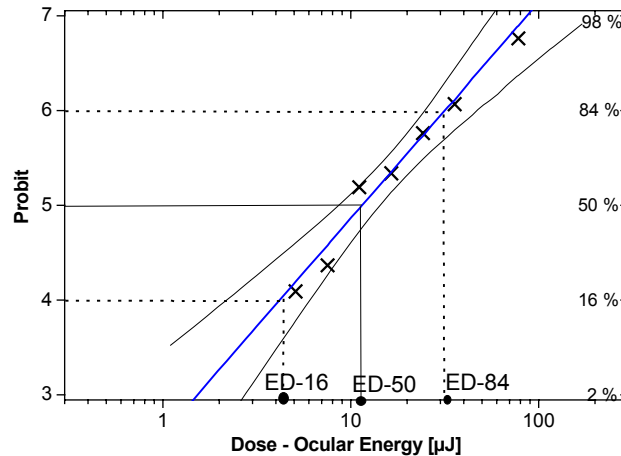


Figure 4. After a probit transformation of the response scale of the data as presented in figure 3, the log-normal distribution becomes a straight line which facilitates graphical fitting and analysis.

A probit value of 5.0 occurs at a probability value of 50 %. A probit value of 6.0 corresponds to ED84 and a probit value of 4.0 occurs at ED16. Data points with 0 % and 100 % response are not shown on a probit scale, as these probability values are not defined on a probit scale. The technique of probit analysis of data is used so widely in laser threshold studies that the term probit plot is used, somewhat erroneously, even when the ordinate is plotted as percentage rather than as probits. Also shown in figures 3 and 4 are the 95 % confidence intervals as calculated by a probit regression.

The most cited point on the probit plot is the ED50. This value is frequently referred to as the "threshold," even though there is *no* sharp threshold and some experimental damage points exist below this "threshold." In order to relate the full information of the variability, the slope is at least as important as the ED50 point, and Mush⁷ even argues that "The extent to which ED50 has been used in the past for assessing the safety of substances could almost be termed as abuse".

It is noted that the original definition of the slope as applied in the classic text of Finney¹⁰ is the conventional mathematical meaning of slope, i.e., the change in probability of an effect divided by the change in dose. Also, some software packages, for instance SAS/STAT, use this definition for the slope for the probit regression analysis, and therefore some laser threshold studies also specify the slope in that way and call it "real slope", RS. The real slope and the slope S are related by

$$RS = 1/\log S. \tag{3}$$

A slope S of 1 corresponds to an infinite real slope, a slope S of 1.1 is a real slope of 24.2, and both are equal for a value of about 2.5. Some other values are listed in table 1.

Table 1. A list of corresponding values for the slope S (multiplicative standard deviation) and the "real slope" RS of the probit plot.

| Slope S | RS |
|---------|----------|
| 1.0 | Infinity |
| 1.1 | 24.2 |
| 1.2 | 12.6 |
| 1.4 | 6.8 |
| 1.6 | 4.9 |
| 2.0 | 3.3 |
| 2.5 | 2.5 |
| 3.0 | 2.1 |

2. DISCUSSION

When the dose-response curve is obtained from a number of exposures to animals in an experiment, the response scale is defined as relative frequency, i.e. total number of exposures producing an effect with a given dose, divided by observed lesions. When a log-normal distribution is fitted to the data, this function can be interpreted as characterizing the probability that an exposed individual will have a threshold less than the dose under consideration, i.e. will suffer an injury for a given dose.

An observed distribution has a spread whose range might be due two sources of dispersion. One is solely due to variability, and the distribution gives the probability that an individual will have their threshold lower than the dose under consideration. Thus the probability is in respect to what damage threshold the exposed individual and exposed site has. Each individual or site has a given specific sharp threshold, and each time the threshold is exceeded, injury occurs. For this pure sense of variability, for each exposure to a given individual and a given site with a given (known) threshold dose, there is no randomness in the response. The dose-response curve in the sense of biological variability represents the fraction of the population where a given dose produces a lesion, hence in this sense, the term “frequency of response” is more appropriate than the term “probability of response”. For instance if the frequency of response, calculated from the dose-response curve, is 10^{-4} , this means that it is expected that in a population of 10 000 there is one individual which has a threshold lower than the respective dose. An interpretation of the ordinate as probability is possible, in the sense of the probability that exposure occurs to an individual who has an individual threshold lower than the dose under consideration. The authors would like to stress the difference of a probability distribution describing biological variability from a probability distribution describing aleatory, i.e. stochastic uncertainty, as used to calculate the probability that a thrown dice shows 6. When a dose-response curve is used in the mathematical sense without considering the background of biological variability, it might be erroneously interpreted to characterize a stochastic probability in the sense of “let’s throw a coin, does a lesion develop or not”.

Besides this interindividual variability, there is another source of variation, which arises because some laser injuries might be induced by stochastic mechanisms. For example, in cases of exposure to ultrashort pulses where the development of optical breakdown might play a role, the probability has the sense of an uncertainty for damage to develop for each exposure of a given individual. Thus, for each specific member of the population and for a given exposure level and site, there is a certain stochastic probability that an injury will occur, like flipping a coin for each exposure.

For thermal, thermomechanical and macroscopical photochemical laser injury mechanisms, which apply for pulse durations greater than about 10 ns, there is very little or no stochastic effect. The following discussion therefore assumes that the stochastic effect is negligible in comparison to inter- and intra-individual variability and other uncertainty components which broaden the distribution.

One main source of an increased spread of the observed distribution is the uncertainty associated with the experimental techniques, including systematic errors. These experimental uncertainties are discussed in Reference 1 of these proceedings, and are summarized and commented from the viewpoint of PRA in the following paragraphs.

2.1 Severity of the consequence

A quantitative risk analysis needs to include a characterization and specification of the severity of the injury for which the probability or frequency is determined. The endpoint in typical laser threshold studies is the minimal visible lesion, MVL, which can be described as a just barely detectable lesion. If the method of examination is ophthalmoscopic, then the endpoint is also called minimal ophthalmoscopically visible lesion, MOVL. However, the severity of the injury depends not only on the level of the ocular exposure, but also on the location of the lesion, as a lesion in the fovea can result in serious vision loss, but may even go unnoticed if located in the periphery of the retina. For a PRA model, the level of severity typically adopted is the MOVL.

2.2 Experimental protocol, comparison with data for humans

Sliney et al. (2001), these proceedings¹, consider whether the results of experimental threshold studies can be influenced by the choice of examination technique and the time of examination. Some techniques are considered more sensitive than others, i.e. for some studies¹², where both ophthalmoscopic examination and histology with microscopy was performed, the ED50 as determined with microscopy was somewhat lower. In other recent studies (for instance exposure to 650 nm, 0.25 s radiation) it was noted that “damage was not detected microscopically at exposed sites not exhibiting an ophthalmoscopically visible lesion” (Ref. 13). Some types of lesions take longer to develop, i.e. the dose-response curve will shift to lower doses for examination at 24 hours after exposure in comparison to an examination at 1 hour after exposure, while Lund et al. in a recent study with blue and green wavelengths and nanosecond pulse durations (Lund, these

proceedings¹⁴) reported that the difference between the ED50 values for 1 hour and 24 hour data was practically zero for most wavelengths which were studied. Also different sites of the retina exhibit different sensitivities: the macula is generally more sensitive due to a higher pigmentation and therefore higher light absorption than the paramacula region. Therefore, when the dose-response curve is determined in the paramacula region with an ophthalmoscope after 1 hour of exposure, the resulting dose-response curve, depending on the type of exposure and lesion, may be about a factor 2 to 4 above a curve which was determined for the macula, 24 hours after exposure and with microscopy. Animal experiments give ED50 values that are generally lower than those for the few studies where human volunteers were exposed. In particular, Ren-yuan et al.¹⁵ reported for experiments on human Chinese retinas for 150 μ s 1.06 μ m radiation a factor 1.8 higher for human vs. grey rabbit and a factor 6 for human vs. rhesus monkey. Vassiliadis et al.¹⁶ reported a factor for human vs. rhesus monkey of about 3 for 100 ms 488 nm radiation, a factor greater than 10 for 200 μ s 694 nm, a factor of greater 3 for 20 ns 694 nm, and a factor of greater 10 for 30 ns 1.06 μ m radiation (the experimental data for humans are rather limited and were not sufficient to perform a probit analysis). Gabel et al.¹⁷ compared ED50 values of chinchilla rabbits to those obtained from human volunteers and obtained a factor of 4 for 488/514 nm 20 ms radiation. In summary, it seems that the higher ED50 values obtained for human exposure, depending on the experimental protocol used to determine the animal dose-response curves, either provide a safety margin or compensate for less sensitive experimental animal experiment protocols. Generally, rhesus monkeys provide a good model for human exposure. However in terms of variability and uncertainty of the variability, i.e. uncertainty of the ED50 and slope and of the shape of the dose-response curve for small probabilities, additional sources of uncertainty, such as varying spot sizes due to focussing errors, need to be considered, as will be discussed below.

2.3 Significance of slope

The slope S is a direct indication of the variability which is expressed by the dose-response curve. It is interesting to note that for medical phenomena which are well described by a log-normal distribution, such as latent periods of infectious diseases and survival time after diagnosis of cancer⁹, the median of the distribution (which is the ED50 for dose-response curves) strongly depends on the kind of disease or cancer, ranges from hours to years, but the slope parameter is a typical value for the phenomena under consideration, i.e. the slope is the same for all diseases or cancers⁹, as is summarized in table 2.

Table 2 Examples of log-normal distributions from medical sciences (adapted from Limpert et al.⁹)

| Phenomena | Median (comparable to ED50) | Multiplicative standard deviation (slope S) |
|---|--|---|
| latent periods of infectious diseases | Hours to years, depending on kind of disease | 1.5 |
| survival time after diagnosis of cancer | Months to years, depending on kind of cancer | 3 |

For laser induced MVL data, the ED50 strongly depends on the wavelength, exposure duration and on the spot size¹². As there are thermal, photochemical and non-linear damage mechanisms, it would stand to reason that there is an inherent typical slope value for each damage mechanism, even though the ED50 can vary over orders of magnitude depending on wavelength and exposure duration. Unfortunately, it seems that the available data are influenced by uncertainties which mask the expected characteristic intrinsic slopes.

2.4 Variability and uncertainty

For laser induced damage, variability, as quantified by a more or less shallow slope of the dose-response curve, can have different origins. Generally, any interindividual variability of physical and physiological properties which influences the threshold for damage, results in a variation of thresholds for a given "population".

An example of interindividual variability is that of the transmissivity and absorption coefficient of the involved tissues: young individuals will have better transmissivity of the cornea and the lens in the blue and near UV than older ones. These parameters can also vary for a single individual in respect to different exposure locations, for instance for different locations on the retina – these variations can be called "intra-individual variability". Also within a given region of the retina, there is a variability of the absorption characteristic due to melanin granules (see Reference 1).

Additional to the biological variability within a given population, experimental uncertainties will introduce a larger spread of the experimentally determined dose-response curve, for instance:

- Uncertainties in the dosimetry, i.e. in the determination of the laser energy, can broaden the dose-response curve.
- Uncertainties in the spot size diameter. The threshold for retinal damage depends on the area of the irradiated spot when the dose is given as ocular energy. Therefore, if for instance an experiment is designed to produce minimal spot sizes, but not every exposure achieves a minimal spot size, then this produces a larger slope, as is discussed below.

It is important to characterize these uncertainties and to attempt to correct the experimental dose-response curve, when it is to be used to characterize the risk for eye injury of a human. Since there are many factors which influence the dose-response curve for laser induced ocular damage, and the influence of the individual factors is usually poorly characterized,

there will be some degree of uncertainty associated with the shape of the dose-response curve which truly characterizes the biological variability of the population under consideration. In particular, if the log-normal distribution is used to quantify the probability for response to a given dose, then the two parameters of the log-normal distribution, the ED50 and the slope will have an associated uncertainty, which can be modeled by probability distributions.

2.5 Confidence intervals

Since the dose-response curve is derived as statistical regression of data obtained with a limited number of exposures, i.e. of a small part of the total population, confidence intervals (CI) describe the range of possible dose-response curves which are the true dose-response curve for the whole population. For instance, the 95 % CI of the ED50 is a range of values, where one can be 95 % sure that the CI includes the ED50 of the whole population. In this sense, the confidence interval gives some information about the uncertainty of the dose-response curve, but with the important assumptions that the examined group of animals (the sample) is representative of the whole population and also that the measurements and the experimental data are exact, and that there are no systematic errors. Our analysis shows that for laser induced MOVL studies, these assumption might often not be valid, for instance if refractive errors exist. It is noted that confidence limits are called fiducial limits by Finney, with the rather cryptic note¹¹, that they are most of the time identical to confidence intervals. So far, no other reference could be identified which also refers to fiducial limits and which would elaborate on the possible differences to confidence intervals. For the application for laser threshold studies, it seems justified to interpret Finney's fiducial limits as confidence limits.

2.6 Experimentally determined slopes

For laser thresholds, corneal dose-response curves have generally very steep slopes, of about 1.1 (e.g. Ref. 16). In some studies of corneal damage, for instance with pulsed CO₂ laser radiation¹⁸, there was a sharp threshold which varied by less than 10 % and therefore no probit analysis was undertaken. A variation within 10 % corresponds to a slope of about 1.1. For retinal studies, however, the reported slopes vary from very steep slopes of 1.01 and 1.05 (Ref. 20) of recent studies to slopes as large as 2.8 for the data presented in figure 3. Also in a study by Lund et al.²¹, a Ti:Sapphire laser was used to produce dose-response curves for 27 wavelengths from 692.0 to 1010.0 nm with a pulse duration of 100 ms, and the slopes varied from 1.11 to 1.59 in what seems like a random manner. Since the wavelength dependence stems from transmission and absorption properties of the ocular media, which determine the energy deposited in the retinal pigment epithelium, and the process is purely thermal, one would not expect a strong change of biological variability from one wavelength to the next.

2.7 Grouping of individual dose-response curves, variability of absorption

Experimental slope values for "surface" laser injury such as to the cornea or the skin, are usually about 1.1. Such a slope would characterize a distribution where 68 % of the distribution lies within a dose range of approximately ± 10 % around the median point, the ED50^{***}. Since the deposited energy, and hence the exposure dose, necessary to produce a given temperature rise depends directly on the absorption, biological variability of the absorption will also result in variability of the threshold, and this is reflected in the dose-response curve. For retinal exposure, the biological variability of the absorption within one macula for the smallest image spot size is of the order of ± 5 % to ± 20 % (Gabel et al.²²), which would correspond to a dose-response curve slope of about 1.05 to 1.2. These values are also supported by graphical pixel density analysis of a flatprep of a human RPE which was prepared by Gabel et al.²², where the analysis with a spot size (averaging area) of 25 μm , 40 μm and 75 μm resulted in a relative standard deviation of 16 %, 11 % and 8 %, respectively.

However, there is also substantial inter-individual variability in respect to absorption properties of the retina, which is estimated to be of the order of a factor 2 (Gabel²², Sliney¹), and this variability is characterized by a dose-response curve with a correspondingly shallower slope.

The applicability of a dose-response curve which characterizes the variability within a given population, and which might be used to indicate the risk, is discussed with the following example: consider that the dose-response curve for a given individual has a slope of 1.1 and the individual ED50 is inversely related to the (mean) retinal absorption of that individual: a small absorption will result in a larger individual ED50 than for an individual with a high absorption, where a smaller dose is sufficient to cause injury. When threshold experiments are conducted with a group where the absorption varies within the group over a certain range, and the data of the whole group are pooled to perform the probit analysis, then a shallower slope with an intermediate ED50 will be the result, as is schematically shown in figure 5.

*** As discussed above, the slope is a multiplicative standard deviation of the log-normal distribution, in contrast to the additive standard deviation as defined for a normal distribution. For simplified comparisons and small values of slope S, such as 1.1, the difference between the additive and multiplicative standard deviation is not large (as the difference between the normal and log-normal distribution is not large) and a slope of 1.1 can be compared to a (additive) standard deviation of ± 10 %.

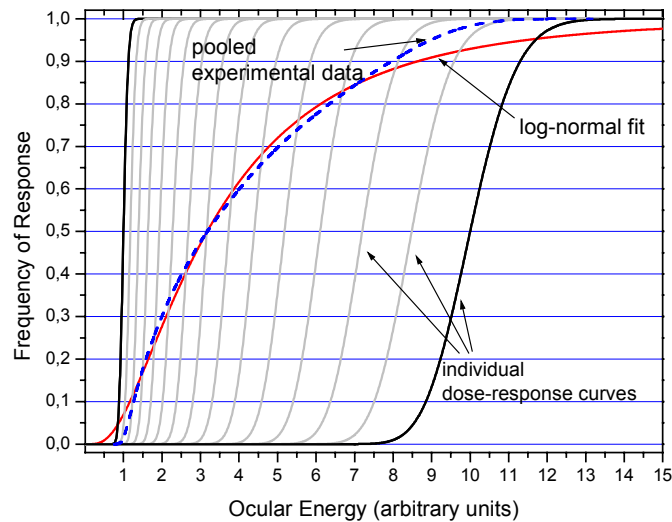


Figure 5. Combination of dose-response curves with steep individual slopes to an overall dose-response curve. Both the combination of simulated pooled data is shown (dashed line) as well as a log-normal curve which is a best fit to the simulated “experimental” data.

The data in figure 5 were derived by simulating individual dose-response curves each with a slope of 1.1 and a range of ED50, starting from ED50 = 1, up to an ED50 = 10 (arbitrary units). The individual dose-response curves were assumed to be continuously overlapping, i.e. the number of individuals within the range of ED50s was assumed to be high, in order to obtain a smooth overall dose-response curve; in figure 5, only 15 individual dose response curves are shown. When the data stem from a small number of non-overlapping individual dose-response curves, the resulting pooled frequency data curve (i.e. the overall dose-response curve) would show steps with horizontal sections where the individual dose-response curve’s data do not overlap. For the simulation of the data shown in figure 5, the distribution of the individual dose-response curves was assumed to be logarithmic, i.e. the logarithm of the individual ED50 values was uniformly distributed. A simulation of the pooling of the dose-response curves was performed by creating random dose numbers corresponding to the individual log-normal distributions as well as the logarithmic distribution of the individual dose-response curves. This simulation technique is akin to laser retinal threshold studies where “injury” – “no-injury” data are recorded for a number of exposures per eye and for a number of experimental specimen, and the data are pooled for all animals as the data from single eyes usually are not usually sufficient for an probit analysis or the construction of a dose-response curve. The resulting pooled data are shown in figure 5 as well as a log-normal distribution which has the same ED16, ED50 and ED84 values as the pooled data. It can be seen that within the approximate range of the ED10 to ED90, the log-normal distribution fits well to the pooled individual data, but deviates for the low and high-dose end of the distribution. When the ED50 values of the individual dose-response curves were simulated to be uniformly distributed, instead of logarithmically, then the resulting pooled data were described better by a normal distribution than by a log-normal distribution, i.e. for that case a log-normal dose response is not an appropriate distribution to describe the variability of the population. For laser induced damage, it is difficult to theorize whether the distribution of individual thresholds (i.e. individual dose-response curves with steep slope) is closer to a uniform or to a logarithmic distribution. For instance with the inter-individual variability of ED50 values resulting from refractive errors (as discussed below) it might be the case that there are more individuals who only have a small deviation from perfect vision and only a few who have strong myopia. In this case the distribution would be best described as logarithmic.

As can be judged from a plot like that shown in figure 5, it seems appropriate to describe the variability within the population with a log-normal dose response for the range between the ED16 and the ED84. For doses above the ED84, the log-normal dose response curve with a slope S equal to the slope S of the pooled data, *underestimates* the frequency of ocular damage for a given dose. The pooled data show a frequency of 100 % for a dose of about greater 11, where the log-normal distribution has a frequency of 94 %.

On the other end of the dose range, the log-normal dose-response curve as fitted to the pooled data grossly *overstates* the variability and therefore the risk for doses less than about the ED16. This can be better examined on a logarithmic scale, as shown in figure 6. Towards the lower dose range of individual response curves, the pooled data are governed by the “yes” data (detected lesions) from the individual with the lowest ED50, i.e. for the example of variability of absorption, by the

individual with the highest absorption. It is important to note that there is a lower boundary for the laser threshold variability due to absorption, as there is an upper bound to absorption: in principal, the theoretical maximum absorption is 100 % of the incident radiant energy – a higher absorption is not possible and the corresponding ED50 is the lowest theoretically possible, limiting the variability on the low dose side (assuming that all other parameters are equal).

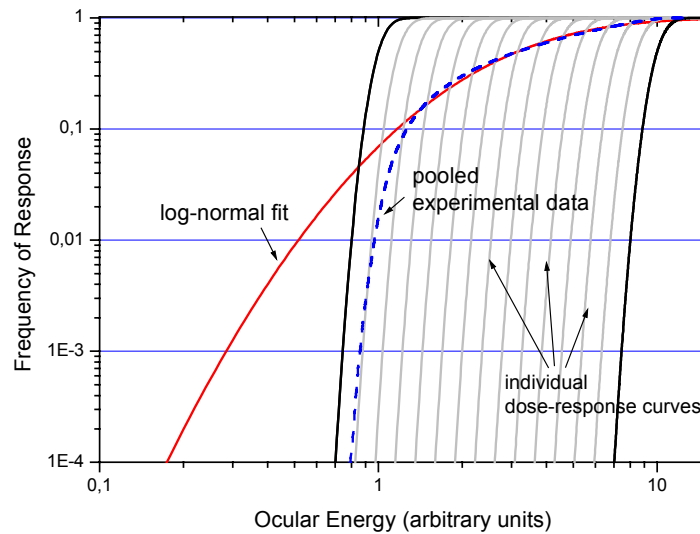


Figure 6. The dose-response curves of figure 5 shown with a logarithmic response and dose scale. It can be seen that for dose values below values where the lowest individual is governing the pooled data, the shallower overall dose-response curve predicts frequencies for response which are far too high.

It is obvious that a log-normal dose response curve which is obtained from pooled data of a population with individual steep dose-response curves but with some variability of individual ED50 values, should not be used to characterize the frequency of response for doses below a certain cross-over point of the log-normal dose-response curve with the pooled data. This crossover point depends on the distribution of the individual ED50 values and on the method of analysis. If the shallower overall dose-response curve were used below the cross-over dose, then the calculated probability values for injury are too large: with overall dose-response curves with shallow slopes, finite probabilities are calculated, for example 10^{-4} for a dose of 10 % of the ED50. Thus a scenario can be envisaged, where 100 000 people are exposed to laser radiation of that dose, and the PRA predicts that ten people would suffer eye injury. If the appropriate steep dose-response curve is applied to this low-dose part, then for a dose of 10 % of the ED50, the calculated frequency for ocular injury would be practically zero. Therefore, for small doses, it is rather the steep individual dose-response curve of the individual, which should be used to quantify the risk.

2.8 Focussing errors

The same arguments as developed above for varying absorption hold for refractive errors: threshold studies are designed to yield a dose-response for a given wavelength, pulse duration and retinal spot size. Often the set-up is for a minimal retinal spot size of about 10 - 20 μm . Due to experimental difficulties, the actual spot size might not be minimal, and has the potential to vary from exposure to exposure, as, for example, when an animal exhibits a refractive error, which may vary during the experiment. If one attempts to obtain a minimal spot size, any refractive error will result in an increased spot size, which leads to a smaller retinal radiant exposure. If a dose-response curve were to be assigned to an animal where a minimal spot is achieved, then the corresponding ED50 will be smaller than for an animal where the energy per pulse is distributed over a larger retinal area, and correspondingly more energy is needed to produce an injury. Rhesus monkeys used in laser threshold studies are usually screened so that the refractive error is not larger than 0.75 diopters. The situation is fully equivalent to the discussion of absorption, when a group of animals is considered, where the refractive error for instance ranges from zero to 0.75 of a diopter. If the threshold is assumed to be varying with the exposed area, then the factor between the threshold for a 10 μm spot and a spot resulting from a refractive error of 0.75 diopter is about 96. If the threshold is assumed to vary with the diameter of the exposed area, as is currently expressed in the laser exposure limits by the factor C_E (ANSI Z136.1) and C_6 (IEC 60825-1), then the factor between zero refractive error and 0.75 diopter is about 10. Values for other refractive errors are given in table 3.

It should be noted that if the refractive error in a given group of experimental animals is assumed to vary between zero and 0.75 diopter, the linear factor 1 to 10 describes the *total range* of individual ED50. The factor from the lowest individual ED50 (corresponding to zero refractive error) to the ED50 of the overall dose-response curve is equal to the square root of

the total range, assuming that all individual data contribute to the overall pooled curve to the same extent. For the example of a refractive error of 0.75 Diopter and a corresponding total range of 10, the increase of the ED50 would be about a factor 3. As is the case for biological variability of tissue absorptivity, the spreading of the dose-response curve is limited towards the side of low doses when focusing errors are considered as reason for the variability: the irradiated area can not be smaller than the minimum spot size.

Table 3. Retinal diameters corresponding to a minimal spot size for no refractive error and for increasing refractive errors. „Factor linear“ relates the retinal spot diameter for a given refractive error to the diameter of the minimal spot size, and this factor would be applicable also for laser injury thresholds, as the laser exposure limit spot size dependence is linear with the spot diameter. „Factor area“ relates the spot area for a given refractive error to the area of the minimal spot size (which is the relationship of the radiant exposure).

| Refractive Error [Diopter] | Diameter [μm] | Factor linear | Square root of factor linear (factor for overall pooled ED50) | Factor area |
|----------------------------|----------------------------|---------------|---|-------------|
| 0 | 10 | | | |
| 0.25 | 40 | 4 | 2.0 | 16 |
| 0.5 | 69 | 7 | 2.6 | 48 |
| 0.75 | 98 | 10 | 3.2 | 96 |
| 1 | 127 | 13 | 3.6 | 161 |

For the situation of an awake human, where refractive errors are usually corrected and where the eye “automatically” attempts to produce a focussed image, i.e. a minimal spot, only the dose-response curve for the minimal spot size appropriately characterizes the risk for exposure to a collimated laser beam. When the experimental dose-response curve is biased by animals with refractive errors, the resulting ED50 and slope values need to be reduced correspondingly. In this sense, when applied to the human case, the influence of the variation of the experimental animal’s refraction needs to be treated as bias or uncertainty, not as biological variability.

2.9 Correlation of ED50 and slope for pooled data

From the previous discussion it is clear that whenever data are pooled from a group of animals where the intra-individual variability is small but there is some inter-individual variability, the overall dose-response curve will have a larger slope S (i.e., a shallower slope) and a higher ED50 value as would be applicable for the most sensitive individual. Also the log-normal dose-response curve as implied in probit analysis of data might not be the appropriate distribution to characterize the frequency of response, especially for doses outside the region of the single multiplicative standard deviation, i.e. outside the dose range ED16 to ED84. A statistical analysis of a specific set of experimental raw data of laser exposures regarding the shift of ED50 values following pooling of data from dissimilar subjects, and a simulation of data from an assumed dose-response curve, performed by A. Langus et al.²³, also showed that high ED50 values correlate with the bias and the standard deviation of the simulated data.

In order to obtain information on the relationship between the increase of the slope as a function of the total range of ED50s, the log-normal dose response curve for the pooled data was calculated as described in the previous section for a set of ranges of individual ED50 values, starting with a range of individual ED50s from 1-2 up to 1-100. When a logarithmic distribution of the individual ED50s was assumed within the respective range, and the individual slope S was assumed to be 1.1, a “pivot point” of the overall distribution functions was identified at the ED7 dose, i.e. at a frequency of response of 7%; for an individual slope of 1.05 and 1.2, the pivot point shifted by less than 1%.

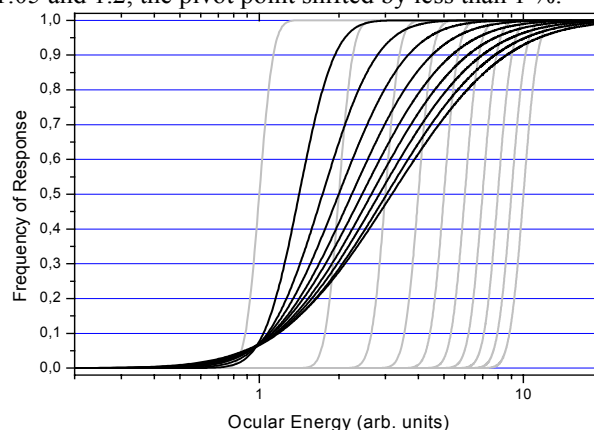


Figure 7. A range of overall log-normal dose-response curves as obtained by grouping of individual data for a set of ranges. The light shaded lines indicate the respective upper ED50 range borders from 2 to 10. The “pivot point” of the resulting overall pooled data response curves is at a response frequency of 7%.

The relationship of the slope to the range of variation of the individual ED50 is shown in figure 8 and representative values are given in table 4. Both the total range of individual ED50s as well as pooled data ED50 are given in table 4, and they are simply related by a square root dependence. Since the lower range boundary is an ED50 of 1, the upper range boundary can also be interpreted as a general multiplication factor for ED50 values. For instance if the total range of individual variability is described by a factor of 4, then the ED50 of the pooled data will be a factor of 2 above the lower range of individual ED50s, and the slope will increase from the assumed individual value of 1.1 to a slope of 1.6.

Table 4. Calculated increase of slope, from a value of 1.1 for an ED50 of 1, with increasing range of variability of the pooled data.

| total range; individual ED50 _{max} / ED50 _{min} | Factor ED50 _{pooled data} / ED50 _{min} | Slope |
|--|---|-------|
| 1 | 1.0 | 1.10 |
| 2 | 1.4 | 1.27 |
| 3 | 1.7 | 1.45 |
| 4 | 2.0 | 1.60 |
| 5 | 2.2 | 1.73 |
| 6 | 2.4 | 1.83 |
| 7 | 2.6 | 1.93 |
| 8 | 2.8 | 2.03 |
| 9 | 3.0 | 2.11 |
| 10 | 3.2 | 2.18 |
| 15 | 3.9 | 2.50 |
| 20 | 4.5 | 2.77 |
| 30 | 5.5 | 3.15 |

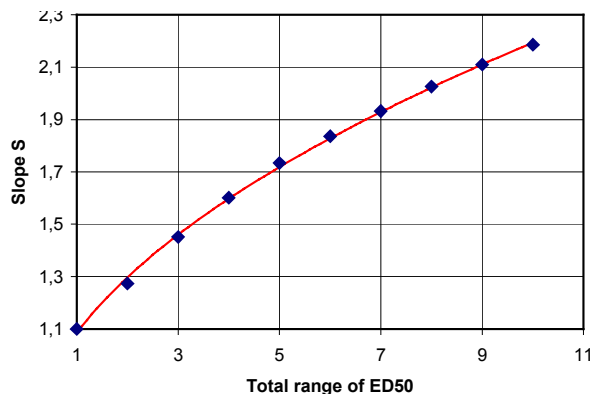


Figure 8. Relationship of slope S of the log-normal dose response curve to the range of ED50 values, where the range is defined as starting from an ED50 of 1 and extending up to the number as given in the plot.

The pivot point and the relationship between the ED50 and the slope also has an application in quantitative risk analysis. Consider the situation where the reported experimental data are derived from pooled data where the individual ED50 varies over a given range, for instance due to focussing errors. Consequently, the experimental dose response curve should be corrected for this variation to obtain a dose response curve which is applicable to a population without this variation (for instance where a minimal spot can always be achieved, as is to be assumed for human exposure). For such a correction, the experimental ED50 and slope would have to be reduced, and the results of the simulation and the correlation between the slope and the ED50, could be used as quantitative guideline for this correction.

When the dose-response curve is “rotated” around the pivot point by reduction of the ED50 and the corresponding reduction of the slopes, the pivot point also divides two trends in terms of probability for response. For a given dose above the pivot point, a reduction of the variability, i.e. of the ED50 and slope, produces an *increase* in the probability for response in comparison to a dose-response curve with larger ED50 and shallower dose, corresponding to an increased level of “risk”. For a given dose below the pivot point, a reduction of the ED50 and slope produces an *decrease* in the probability for response in comparison to a dose-response curve with larger ED50 and shallower dose, corresponding to an decreased level of “risk”.

2.10 Small probabilities

In the field of quantitative risk analysis and management, acceptable risk levels are often of the order of 10^{-6} per exposure or less, and scenarios are often evaluated where a larger number of people may be exposed. As a result, probabilities of injury often need to be calculated for doses much below the ED50.

The simulation of the pooling of experimental data showed that for the case of a small intra-individual variability but a certain inter-individual variability in a given population, it is not appropriate to extend the (shallow) log-normal dose-response curve to doses lower than about the ED10. However, even for the case where there is little experimental uncertainty and individual variability, or if the overall dose-response curve is corrected by reduction of the slope and correspondingly the ED50, the uncertainty associated with the lower-dose part of the dose-response curve is substantial. The dose-response curve is not known for such low probability values and in practice cannot be determined, as tens of thousands of weak exposures would be needed (compare the “megamouse experiment”, Ref. 8). Finney¹¹ states that “...very extreme probits, say outside the range of 2.5 to 7.5, carry little weight, and may almost be disregarded unless many more subjects were used...” Probit values of 2.5 and 7.5 correspond to probabilities of about 1 % and 99 %, respectively. It has to be kept in mind that the log-normal dose-response curve describes the biological variation of the sensitivity of different individuals and of different locations of exposures for one individual (for instance different regions of the retina). Applying log-normal dose-response curves down to ever decreasing doses would imply that laser radiation of any level could cause injury, i.e. in a small but finite fraction of the population, be it 1 in a billion or less. However, for the case of thermal damage, simple biophysical reasoning shows that energy levels which do not result in a temperature increase of more than, say, 1 °C, cannot produce an ocular injury. If they did, the temperature elevation of 1 °C typical in a mild fever would cause blindness.

Following biophysical reasoning, for thermally induced damage^{****}, there will be a lower cut-off energy, below which injury is not possible, not even for the most sensitive individual. For PRA, this could be modeled by truncating the dose-response curve at a certain dose, i.e. setting the dose-response curve to zero below a certain ocular energy or exposure value. At present, the knowledge about this lowest possible dose is not sufficient to define such a truncated dose-response curve, but one could model the cut-off point with a probability distribution and perform Monte-Carlo simulation. However, in the PRA model discussed here, this was not done, as the application of steep slopes results in a marked decrease of the probability for damage for very small dose values, in effect similar to a cut-off. For instance, for a slope of 1.1, the calculated probability for the dose value of one 5th of the ED50 is $5 \cdot 10^{-64}$ and for the dose of one 10th of the ED50 could not be calculated with the mathematical software available, but is less than 10^{-100} . Considering that the dose-response curve in the sense of biological variability represents the fraction of the population where a given dose produces a lesion, probability numbers less than the world population do not make sense.

Table 5. Sample values for the log-normal cumulative distribution for a list of slopes, for dose values of a factor 10 and 5, respectively, below the ED50.

| slope | Probability for one 10 th of ED50 | Probability for one 5 th of ED50 |
|-------|--|---|
| 1.1 | < 1E-100 | 5E-64 |
| 1.15 | 5E-61 | 7E-31 |
| 1.2 | 9E-37 | 6E-19 |
| 1.25 | 3E-25 | 3E-13 |
| 1.3 | 9E-19 | 4E-10 |
| 1.4 | 4E-12 | 9E-07 |
| 1.6 | 5E-07 | 3E-04 |
| 1.8 | 5E-05 | 3E-03 |
| 2 | 5E-04 | 1E-02 |

3. MONTE CARLO SIMULATION OF THE UNCERTAINTY OF DOSE-RESPONSE CURVES

A quantitative risk model was developed to predict the probability for ocular injury upon exposure to pulsed laser radiation. The model was set up for pulse durations less than 1 μs, wavelengths between 190 nm and 19 μm using off-the-shelf mathematical software. The ocular damage model is part of a larger risk model which was developed to characterize the probability for ocular injury from space based lasers and possible exposure with telescopes of varying diameter (Schulmeister et al.²⁴).

^{****} Also for acute photochemical damage, there is a minimum dose which is necessary to produce a lesion.

The ocular damage model is based on log-normal dose-response curves, and uncertainties associated with the parameters of the dose-response curve, i.e. the ED50 and the slope, are modeled by sampling these values from probability distributions and calculating the probability of response for a given laser ocular energy for each sample. The probability distributions for the ED50 parameter, with wavelength and pulse duration dependence where applicable, are derived from values as reported for rhesus monkeys, and for the corneal damage thresholds for rabbits. For retinal injury, the potential bias of the reported dose-response curve due to experimental uncertainties, such as focussing errors, were considered by using the lowest reported ED50 values as an upper border of the range of ED50 values, and setting the lower range of ED50 values a factor of 2 below the upper border. Following the discussion above, the slope S is set to vary between a value of 1.05 and 1.4, in correlation with the range of ED50 values, i.e. for the lowest ED50 value a slope of 1.05 is chosen and for the largest ED50 value, a slope of 1.4 is chosen. The distributions of ED50 and slope values are taken as uniform, i.e. with equal probability between the lower and upper possible values.

As discussed above, the slope of the retinal dose-response curve for doses below about ED10 should be set to steep values, for instance of the order of 1.05 to 1.2. In the model the range of 1.05 to 1.4 is generally used for the dose-response curve, thereby somewhat overestimating the risk for exposure to small doses. However, for the scenario of space based lasers, the exposure level of the naked eye at the earth surface is usually well below the ED50, and only for exposure with (large) telescopes, is energy sufficient to cause ocular injury collected. The probability for exposure with a telescope with a relatively small field-of-view is quite small. The overall probability for ocular injury during a given mission is dominated by the probability of exposure with that type of telescope, which has the smallest diameter that results in a high probability of ocular damage (close to 1). For this kind of scenario, the overall risk numbers are not sensitive to the shape of the dose-response curve towards the low dose range. This part of the dose-response curve might however become relevant for a scenario where a large number of people is exposed to laser radiation and the exposure level with the naked eye is in a range closer to the lower range boundary of the ED50.

In the ultraviolet (UV) and far infrared range for pulses with durations less than 1 μs , due to sparse experimental data, the uncertainty associated with the slope is less pronounced than the uncertainty of the ED50 values: from available data for some limited wavelengths which affect the cornea or the lens, the slope can generally be assumed to have relatively little uncertainty and vary in the range of 1.05 to 1.2. However, regarding available data for the ED50, for instance for possible thermal corneal and lenticular damage induced by UV pulsed radiation with wavelengths above 310 nm and pulse durations between 1 μs and 1 ns, the experimental data are very few: the only experimental threshold value for thermal damage of the lens by short pulse laser radiation found in the open literature is for 337 nm nitrogen laser with a pulse duration of 10 ns (Zuclich²⁵). Additional information on thresholds to short pulse exposure in the UV can be obtained by extrapolation from exposure to 350 nm radiation with a range of pulse durations between 100 μs to seconds (Zuclich²⁶) and on the lower exposure level side can be bracketed by data for CO₂ laser radiation, which is absorbed by a small absorption depth in the cornea and can be assumed to be having distinctively lower thresholds than near-UV radiation. For the ocular damage model, the uncertainty associated with respective ED50 values for wavelengths between 310 nm and 400 nm and pulse durations between 1 μs and 1 ns, is represented by a triangular probability distribution with a lower and upper border of 3,000 J m⁻² and 100,000 J m⁻², respectively, and by a most-likely value of 10,000 J m⁻².

The uncertainty of the ED50 and slope is simulated with the Monte Carlo technique, where random numbers are calculated for a given distribution of possible values so that the relative frequency of the calculated values correspond to the respective probability distribution. These lists of values for the parameters of the model are used to calculate the output parameter, such as the probability for ocular damage for a given ocular energy. A histogram of the values for the end result represents the distribution of values for the output parameter under consideration. The general scheme is visualized in figure 9, starting with the log-normal dose-response curve with a certain slope and ED50, where for a given ocular energy value, a single value for the probability for response can be identified (Figure 9 (a)). For instance, a value of 0.78 for an ocular energy of 8 μJ . When the parameters ED50 and slope are treated as uncertain, corresponding probability density distributions are defined (Fig 9 (b)), which vary the ED50 and slope, and thereby the shape and location of the dose-response curve in a given range (Fig. 9 (c)). When the probability for ocular damage is to be determined for the ocular energy E_0 , then instead of a single point for the probability for ocular damage, a frequency distribution for the probability for ocular damage is found (Fig. 9 (d)), representing the cumulative distribution of dose-response curves over the range of probability for ocular damage values, for a given ocular energy.

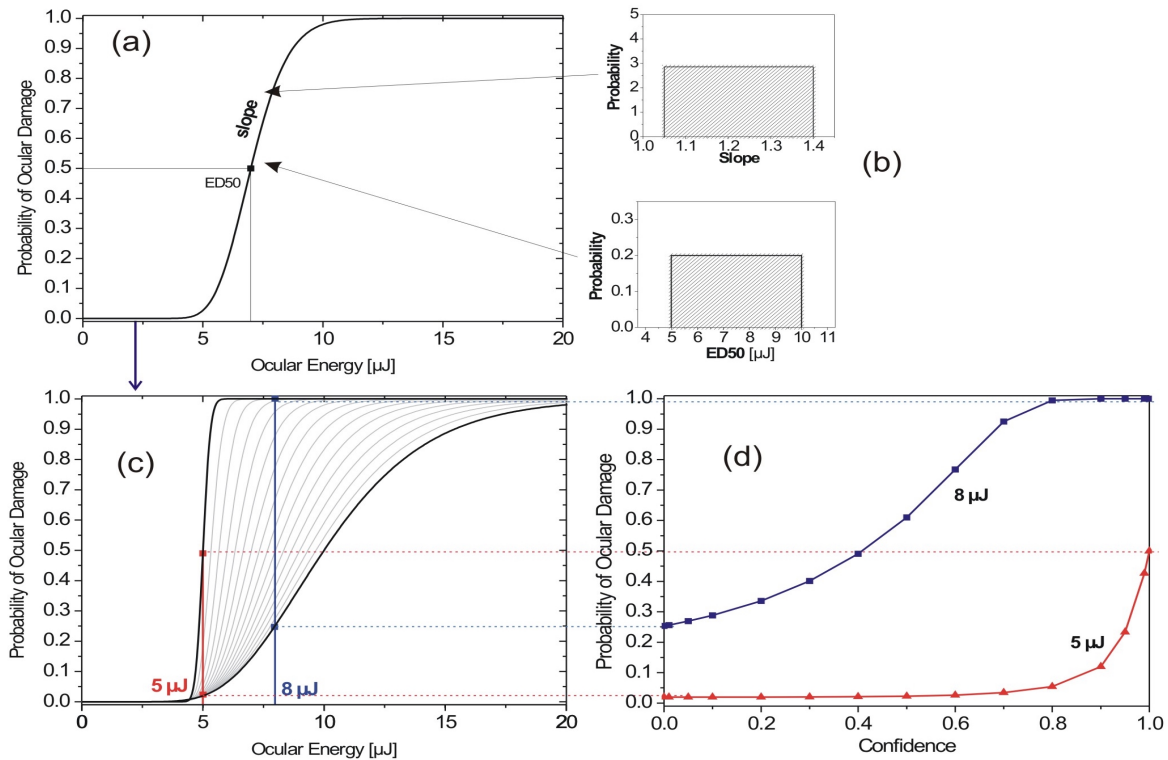


Figure 9 Schematic overview of the calculation of a distribution characterizing the probability for ocular damage given an exposure to a certain energy, and given a certain uncertainty of the shape parameters ED50 and slope S. The arbitrary values of 5 μJ and 8 μJ are taken as examples for the ocular energy.

By simulating the possible range of values for ED50 and slope, the single point value for the probability for ocular damage for a given energy (Fig. 9 (a)) is replaced by a distribution (Fig. 9 (d)). The result of the probabilistic analysis with uncertainty, figure 9 (d), is usually flipped regarding the axis and plotted with the confidence level on the ordinate and the risk figure, i.e. the probability for ocular damage, on the abscissa, as shown in figure 10 for a range of ocular energies. For the example shown in figure 10, a variation of ED50 between 5 μJ and 10 μJ and a variation of the slope between 1.05 and 1.4 for ocular energies between 0.5 μJ and 10 μJ was simulated. These values apply for instance to an exposure to radiation with a wavelength of about 900 nm and pulse durations between about 10 ns to 50 μs radiation with a minimal retinal spot diameter.

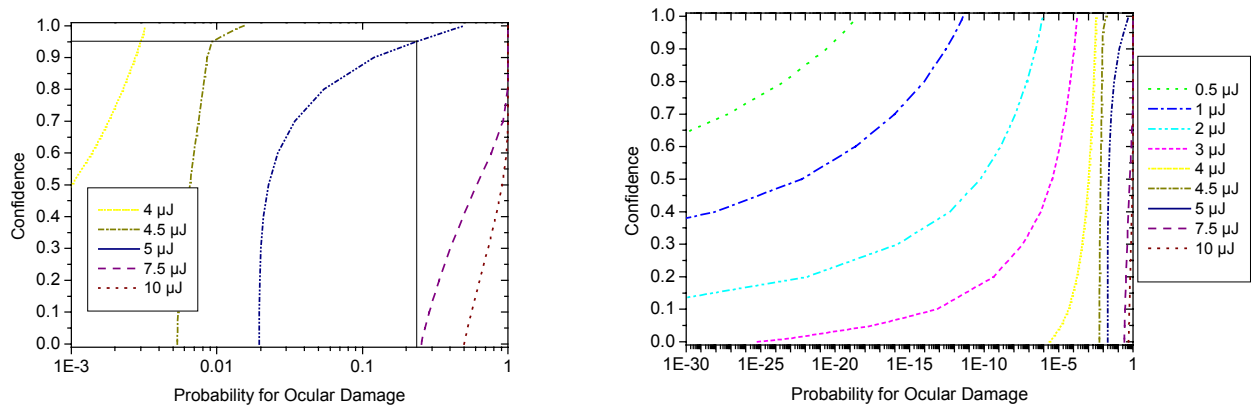


Figure 10. Probability distributions for the probability of receiving ocular injury for a range of ocular energies. The left plot includes ocular energies well below the range of ED50, while the right plot covers a smaller range of probability values.

For plots resulting from the modeling of uncertainty, as shown in figure 10, the ordinate can be interpreted as the “confidence level” for the probability of ocular damage for a given ocular dose. The confidence level can best be explained by an example: in figure 10, with a confidence level of 95 % (the 95 % quantile), the probability for ocular damage given exposure to 5 μJ , is less than or equal 0.23, or 23 %. In other words, there is a 5 % chance that the probability for ocular damage is larger than 23 %. The level of confidence which is used to determine the value on the ordinate is a choice by the risk management. The higher the required level of confidence, the higher the calculated risk numbers become. For instance, if the choice for the level of confidence is 99 %, then one can be 99 % confident, that the probability for ocular damage is less than or equal 40 %. For environmental studies and other risk analysis studies where uncertainty is modeled, often the 95 % quantile is used. The European Space Agency defines a representative quantity of the distribution, called “potentiality” as the logarithmic mean between the 95 % and 50 % quantile. This quantity, attempts to account for both the tail of the distribution towards higher risk numbers as well as the median of the distribution. The model as developed calculates the full set of quantiles, and it is the choice of the user which quantile is used to derive a risk number.

As expected, when exposure to doses within the modeled range of ED50 is considered, the probabilities at the 95 % quantile are high, but decrease for ocular energies which are below the lower border of the range of ED50s. For instance, in figure 10, for 1 μJ (a factor 5 below the lower boundary of the ED50 range and a factor 10 below the upper boundary of the ED50 range) the probability for ocular damage at the 99th quantile is less than 10^{-11} . It should be noted that the distributions for ocular energies below the ED50 range do not have an upper tail towards higher risk values, i.e. the risk hardly increases for levels of confidence above the 95th quantile, and one can have a confidence level of 100 % that the probability for ocular damage is less than or equal to instance 10^{-11} for the ocular energy of 1 μJ .

The above calculations were obtained for a given specified (single point) value for the ocular energy. For many exposure scenarios, the actual level of exposure is not known, or can vary within a given range. In the model as developed for exposure from space based lasers, for instance, turbulence effects in the atmosphere induce scintillation are considered. Scintillation randomly varies the ocular energy around a mean value, which is the exposure level without scintillation, and this can be described by a probability density function²⁷. Also for a given group of the population, the use of different kinds of optical instrument, which have different glass thicknesses and thus transmissivity, or varying atmospheric transmissivity, can be modeled by a distribution, describing the variability of ocular dose within a specified user group. For such a case of uncertainty and variability of the ocular energy, the resulting probability distributions for ocular damage might show a shallower tail towards higher risk numbers.

5. SUMMARY AND CONCLUSIONS

- For probabilistic risk analysis (PRA) of exposure to laser radiation, it is helpful if the concept of biological variability (heterogeneity within a population) is distinguished from uncertainty, i.e. lack of knowledge.
- When applying the dose-response curve for analysis of experimental data (Probit analysis), and especially for PRA, it should be remembered that the basic meaning of the dose-response curve is to characterize the biological variability of individual thresholds. The ordinate of the dose-response curve (the probability for ocular injury) in this sense, characterizes the probability that the exposed individual or retinal location will have a threshold smaller than the exposure level under consideration. If the threshold of the exposed site and individual were known, the situation is deterministic whether or not injury occurs for a given ocular exposure, i.e. there is no random aspect to the development of injury. For some types of laser-tissue interaction, in addition to the variability described by a dose-response curve, there might be stochastic processes involved.
- It is argued that the individual dose-response curve has a steep slope of the order of 1.05 to 1.2, even for retinal exposures. This slope characterizes the variability of thresholds of different sites of the retina.
- Due to inter-individual variability in a given group of experimental animals or population, there can be a spread of individual thresholds. When experimental threshold data is obtained for such a group and the data are pooled, an overall dose-response curve with a larger ED50 and shallower slope is the result. By performing simulation of the pooling, it is shown that the log-normal distribution only represents the pooled data well in the central part of the dose-response curve; it underestimates the risk for doses above the ED84 and grossly overestimates the risk for doses below the ED16.
- The variability of thresholds is limited towards lower doses due to biophysical reasons. Therefore there is a lower cut-off energy, below which the probability for ocular injury is zero.
- Uncertainties and variabilities which are present during the performance of the threshold experiments, and which are not present for the exposure of humans, need to be taken into account when the dose-response curve is used in PRA. When variability and uncertainty, which is bounded at small doses (such as due to variability of absorption or retinal

spot size) is corrected, the slope S and the ED50 need to be reduced. Simulations were performed to identify the correlation between the slope S and the ED50 for pooling of data.

- The uncertainty associated with the dose-response curve, i.e. to the ED50 and slope, can be modeled with probability distributions and Monte Carlo simulation. The result of such a model is a distribution for each given ocular injury, which characterizes the level of confidence about a calculated probability for ocular injury.

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