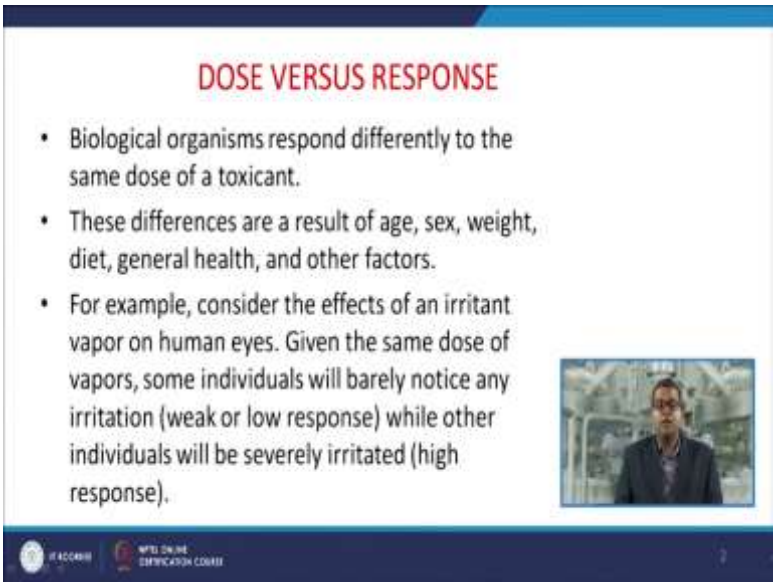
Chemical Process Safety
Professor Shishir Sinha
Department of Chemical engineering
Indian Institute of Technology Roorkee
Module 02
Lecture 08
Dose-Response Relationship

Welcome to this Dose Response Relationship module. In this particular module, we will discuss about the Dose response relationship, in which suppose anybody gets contaminated with any kind of toxic substance, what are the responses, what are the different parameters deals with responses and because this particular information is essentially specially when we need to detoxify or we need to overcome the effect of those toxicant to the human body. It is closely related to our day-to-day affairs, it is closely related to our knowledge to the medicines, et cetera. And one more thing is essential that the knowledge about our body system is quite important in that while we are studying this dose response relationship.

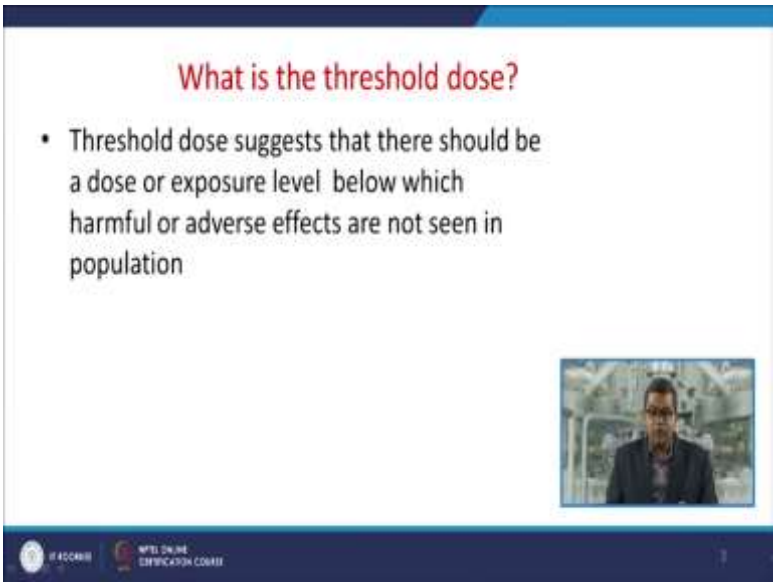
(Refer Slide Time 01:24)



Now, the biological organs they are responsive in different manner to the same dose of a toxicant. In the previous model we discussed that the same type of concentration maybe harmful to the younger people or to the older people, but it may not be harmful to the middle aged people. So these differences whatever differences towards the response they are the result of age, sex, weight or the physical condition, diet, general health and other factors. For example, consider the effect of an irritant vapor on human eyes, given the same dose of vapour. Some individuals will barely notice any irritation, this is very weak or low response while other individuals will be severely irritated, they are the high response.

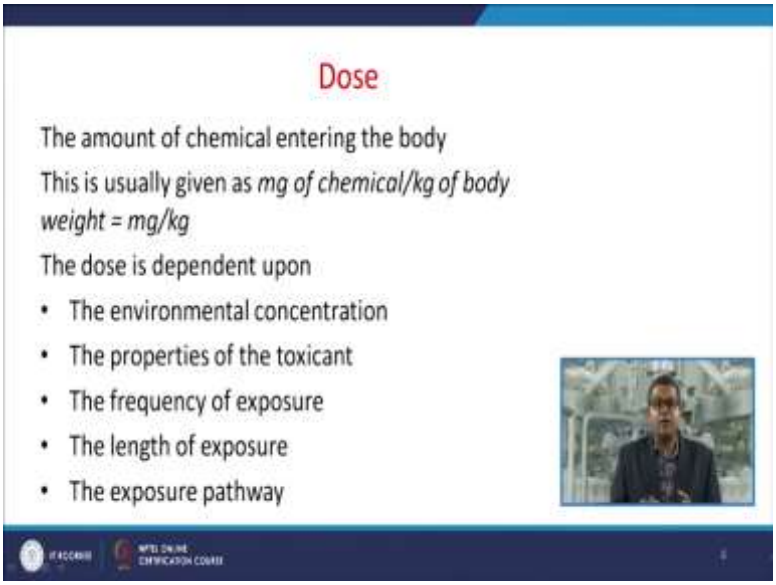
The other factors are like my body is acclimatized, suppose I am working in ammonia and environment, so my body is acclimatized to that particular ammonia concentration which is continuously being released from my workplace, but if a visitor comes then this particular small quantity of ammonia may be slightly irritant to him, so this is clubbed under the other factor. Or sometimes in that particular environment if a small kid comes then it may be even fatal for him, sometimes older people may come then again it may be very difficult scenario for them, so it depends on various factors. So while considering to the dose response curve or while forming dose response relationship you must know that what are the different parameters those who govern this particular type of relationship.

(Refer Slide Time: 3:21)



Now before we go ahead with this type of relationship we must understand that what is threshold dose? The threshold dose suggests that there should be a dose or exposure level below which harmful or adverse effects are not seen in population or in individual. It is just like that if you go to the doctor or a medical practitioner, usually he or she suggest a particular dose for any kind of disease that is purely based on the information available to him that what are the symptoms, what is your age, what is your physical condition, and based on this particular information he usually suggests the dose, maybe OD, maybe BD, once in a day, both time of the day, or in 6 hours duration or 8 hours duration, so that depends on the information available to him and maybe 5MG, maybe 10 MG, et cetera. So he needs to find out that what is the threshold so this particular information is essential.

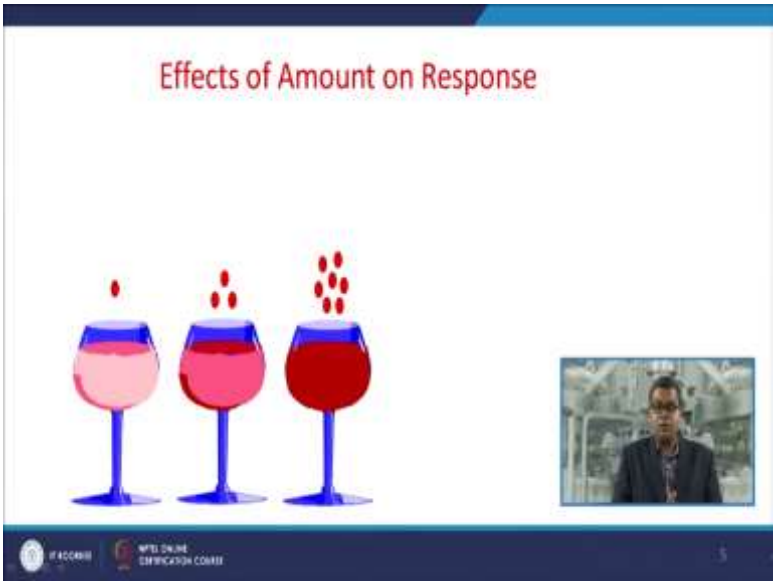
(Refer Slide Time: 4:32)



Now what is dose? Somebody may ask that what is dose. This is the amount of chemical or medicine entering into the body system, this is usually given as milligram of a chemical per kilogram of body weight, milligram per KG. This dose is dependent on environmental concentration, the reason is that suppose you are working in a humid environment then certain chemicals may have very good affinity with water, they may get absorbed into the body system through either dermal absorption or it may enter into your body, you must know that what is the environmental condition, what are the properties of toxicant you may get this particular information from MSDS Material Safety Data Sheet. What is the frequency of exposure, suppose I am working over here, the concentration maybe on the higher side compared to the person who is at the corner of this particular room, so what is the frequency of exposure.

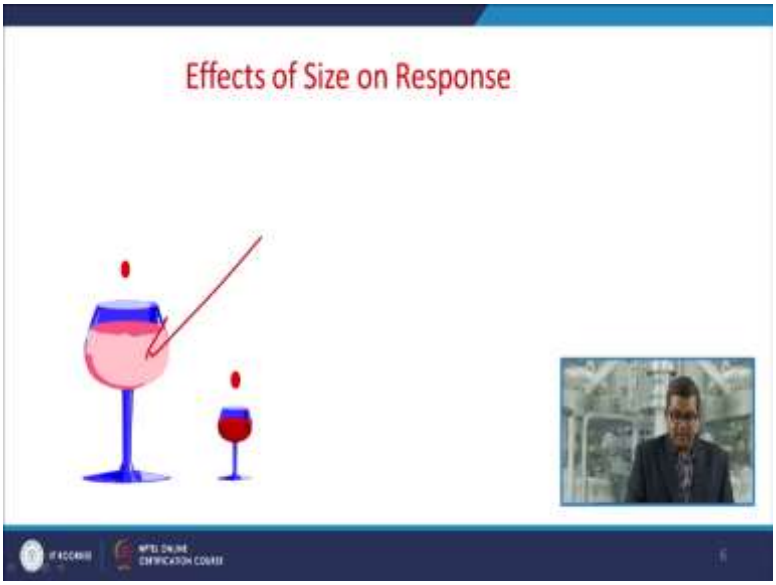
And sometimes I am working over here, I am exposed to the concentrated toxicant and then I go outside to the room for a cup of tea that means the concentration gradually decreases up to the tea mart and then I am coming back, so what is the frequency of exposure? What is the length of exposure? Continuously I am working for 8-hour shift then definitely the exposure will be on higher side compared to intermittent exposure. What is the exposure pathway? That is the route of entry, maybe inhalation, maybe dermal absorption, maybe injestion, maybe some other mode.

(Refer Slide Time: 6:09)



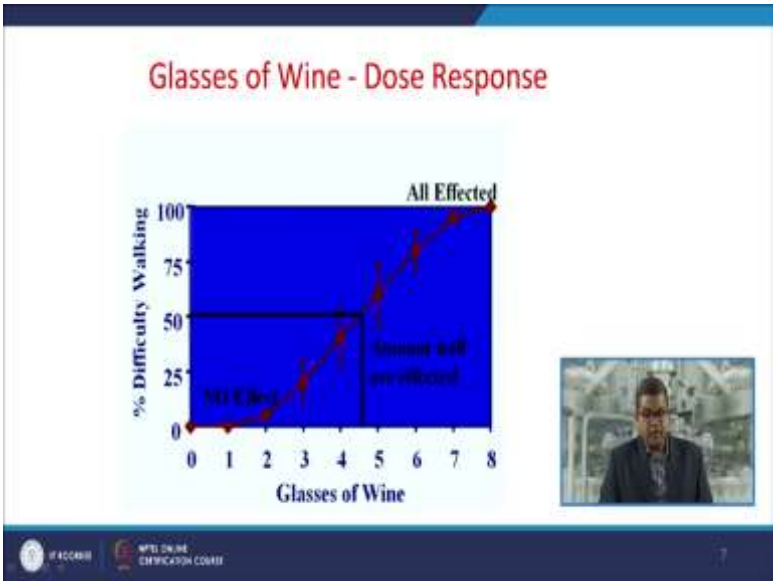
Now this is a very good example that is effect of amount on response. Suppose I am a wine taker, then definitely how much quantity of wine I am taking, maybe small glass, maybe medium or maybe larger one, so how much quantity I am taking in a single dose? Maybe a larger pack, maybe a smaller one or maybe medium one so the response would be different to the body system. Second thing is that how much I am taking in a repeated manner, like suppose I am taking the same quantity up to say 4, 5, 6 different times then definitely the response would be different for a single exposure.

(Refer Slide Time: 7:00)



If it is on the larger size then definitely the response would be different.

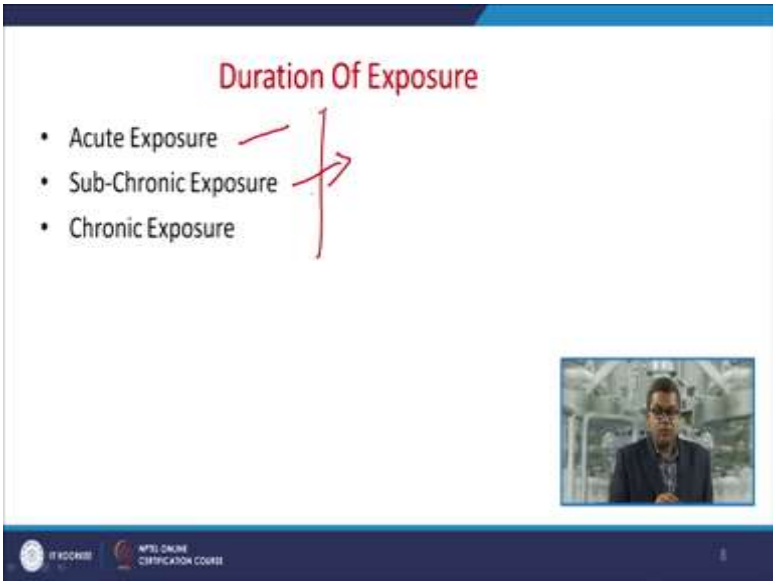
(Refer Slide Time: 7:04)



Now this is a very interesting Dose response curve, suppose you are taking one glass of wine based on your body structure, based on physical condition, you may experience no effect. And if you are acclimatized then obviously in the subsequent glasses you will not see any kind of effect. But if a small kid takes a glass of wine then definitely the effect would be more prominent. Then again you start taking second glass then marginally you will see response, sometimes your voice may fluctuate, sometimes your body language says ok you are drunken and if you take third one then again the effect is on the higher side subsequently. And if you take larger quantity beyond your expectation, beyond your capacity then definitely you will observe all kinds of effects, even sometimes it may become fatal.

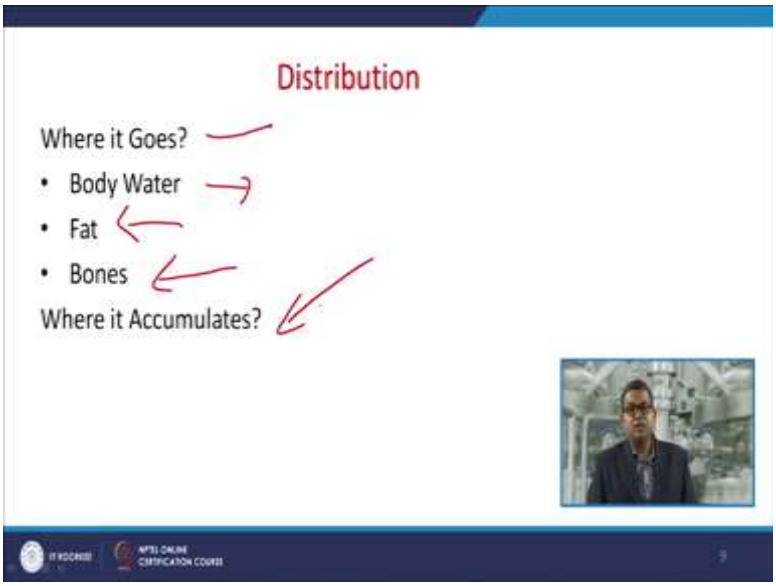
So if you plot the dose response curve with the glass of wine, maybe one parameter of your analysis is the person feels difficulty in walking so primarily you will not see any effect, then slight difficulty in walking, and if you go and sometimes you will fall yourself in a gutter. No doubt, it is a very interesting example, but it gives you prima facie information that how we can create the dose versus response curve. Now in engineering perspective, this Y axis may be different, this X axis may be different. And suppose if you replace this glass of wine X axis with the medicine or with any kind of toxic substance, and this is towards the response to your body system, so primarily you may experience something is irritating, then it goes into the body system then it affects the bloodstream, then it goes for the deposition or detoxification aspect, so you may experience all kinds of effects, so this is the start-up of your formation of dose versus response curve.

(Refer Slide Time: 9:23)



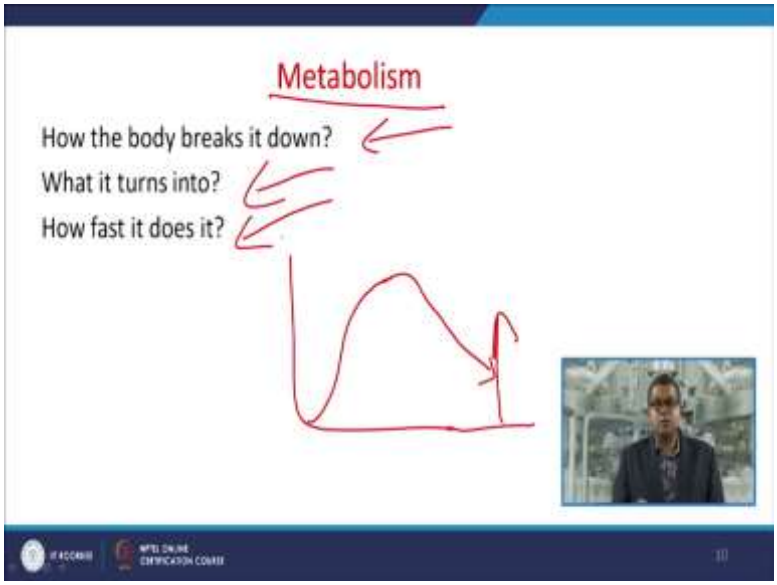
So while creating this dose versus response we must know that what is the acute exposure (we have already studied in the previous module), what are the sub-chronic exposure and chronic exposure.

(Refer Slide Time: 9:36)



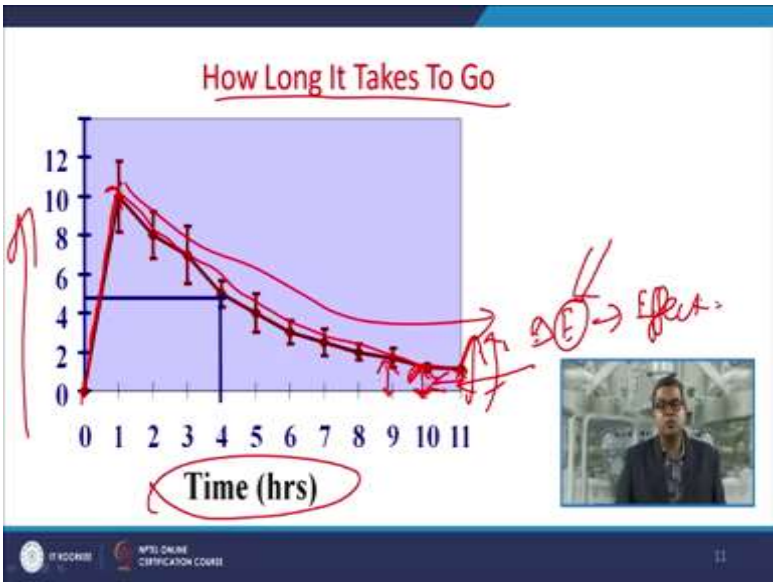
Then we must understand that where it goes? Maybe the body water may become the part and parcel of fat, may get deposited into the bone marrow or may go into the bones, and where it accumulates because sometimes the after-effect is a prominent form of study.

(Refer Slide Time: 10:11)



We must know that how our body reacts in terms of metabolism, how our body breaks it down, it is evenly applicable for different types of medicines. And it is why doctors or medical practitioners they used to suggest that you take this particular medicine for 6 hours, 8 hours, et cetera because their effect will be up to a certain level and there after it may go into downward trend, then again you need to repeat the dose. What it turns into? If you are encountered with a toxicant then after decomposition or after affecting with the body system what it turns into and how fast it is. Sometimes it may create instantaneous problems, sometimes after a day or sometimes after a week or so.

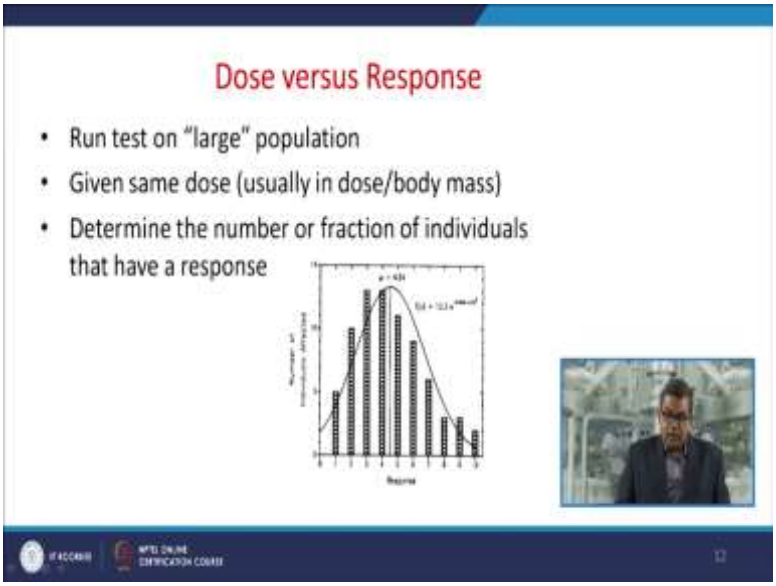
(Refer Slide Time: 11:12)



Then you must analyse that how long it takes to go. Means these are the time, how much time and these are the effects. So at the start of it is just like a medicine theory, at the start-up it works very well and then over a period of time the effect is on the lower side, so at this particular point of time you need to take another dose so that you can have sustainable effect. But it is not true for toxic substance, instantaneously you are taking that toxic substance through four roots of entry instantaneous and then it may take longer hours to decontaminate, detoxify your body system, so you need to find out that what is the deficiency, and deficiency is depicted by this particular Delta E, Delta E is the effect.

So you have to analyse this Delta E because this gives you a very vital clue for your future treatment because whatever toxic substance left it may get deposited into the fatty tissues, et cetera so you need to find out this one because of the inherent ability of our body structure, body system. Our body usually retaliates and it starts the remedial measures immediately after the intake of that toxic substance. So this is the effect where our body fails to retaliate for those particular toxic substance so you need to find out this particular Delta E.

(Refer Slide Time: 12:55)

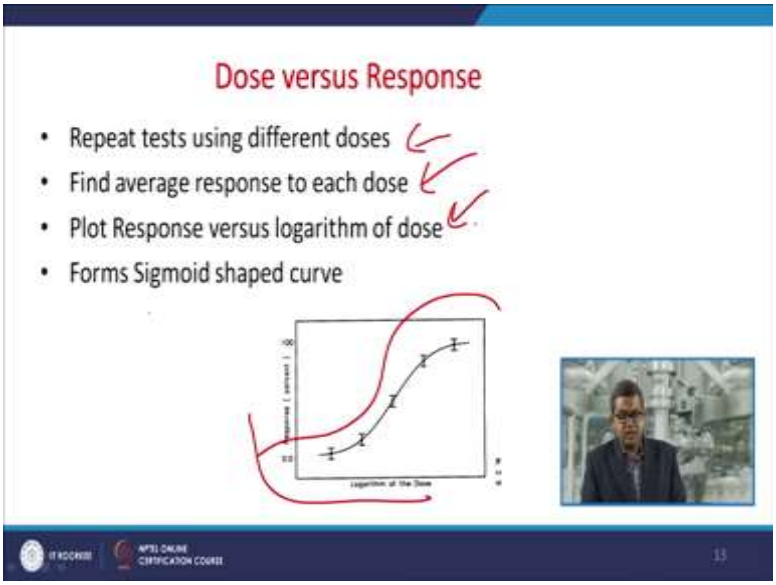


Now usually, whenever we studied the dose versus response, usually it is desirable to run that test on a larger population and to form this Gaussian distribution curve, given the same dose usually in the form of dose versus body-mass. Determine the number or fraction of individuals that have responses because again I am giving you a practical example. When Methyl Isocyanate was released from Union carbide plant in Bhopal, a large concentration of MIC was released to the nearby people of Union carbide, and the effect of that particular concentration

was different to each and every individual because the population was comprises of small kids to older people so the large population was covered under the head.

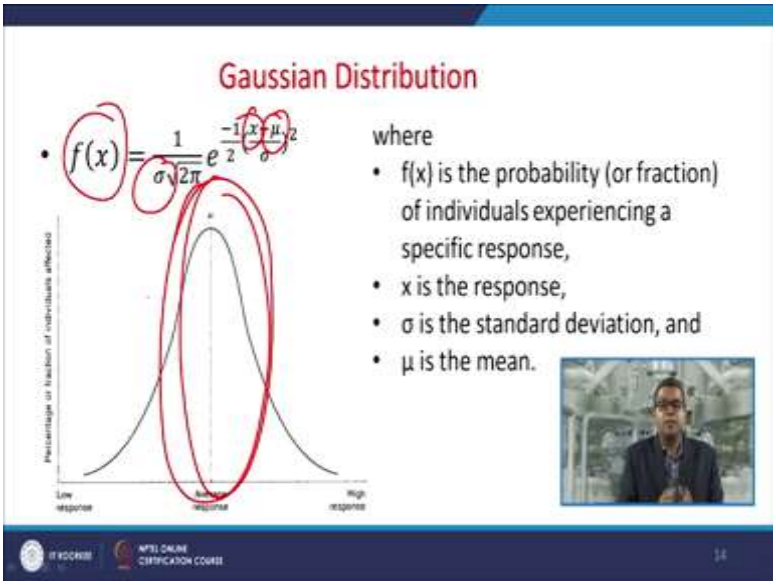
The concentration was common to all, then only thing is you need to determine the number of fraction of individuals that have responses, they may be small kids, 10, 20, 30 percent of small kids, even 10, 20, 30 percent of middle aged people, maybe a larger quantity of old age people. So you need to collect all those responses and number of individuals affected and then you need to form the dose versus response curve so that you can analyse that which population is great affected more compared to this one and compared to this one so that you can start a remedial measure for that particular population.

(Refer Slide Time: 14:58)



Now if your results are not satisfactory then you need to repeat the test using different doses, of course impractical since you cannot do that is why you need to perform this test in laboratory scale. Find average response to each dose, then you plot response versus logarithm of the dose, sometimes you may get this type of Sigma shaped curve and this gives vital information.

(Refer Slide Time: 15:29)

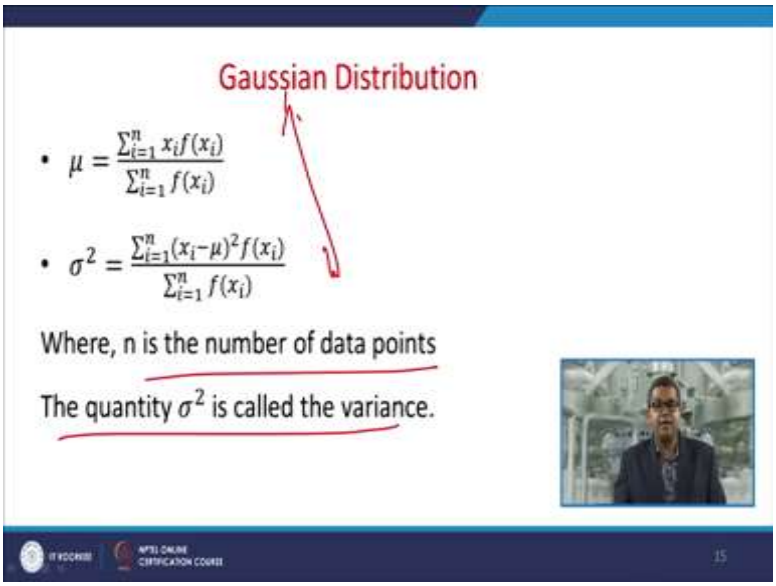


You need to find out the Gaussian distribution with the help of this mathematical formula;

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{-1}{2}(\frac{x-\mu}{\sigma})^2}$$

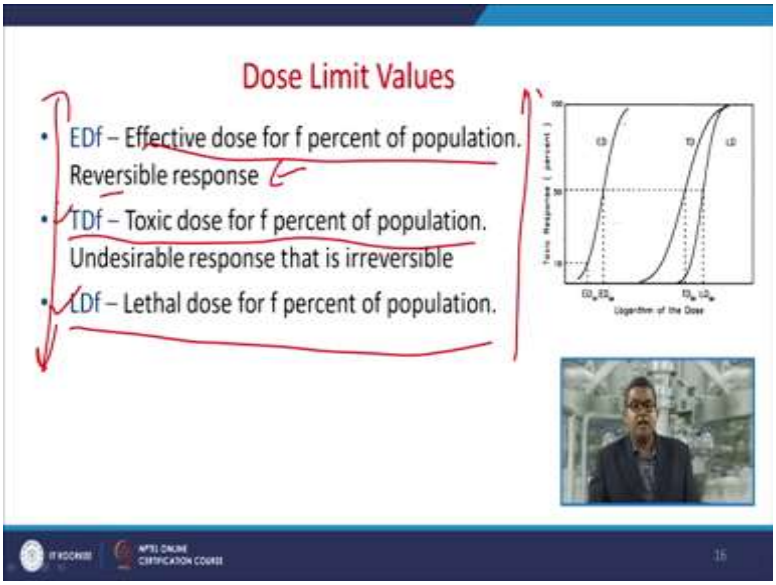
f(x) is the probability or fraction of individuals experiencing a specific response. x is the response, σ is the standard deviation and μ is the mean, so you need to find out and you must know that where these average responses are placed.

(Refer Slide Time: 16:01)



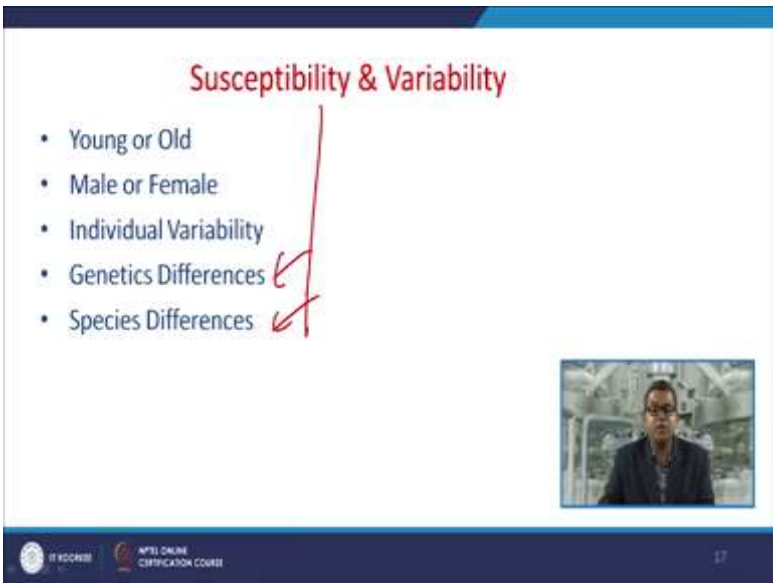
This is the mathematical relationship through which you can find out the μ and σ, and n is the number of data points, how much samples you have collected would, and the quantity Sigma square is called the variance.

(Refer Slide Time: 16:20)



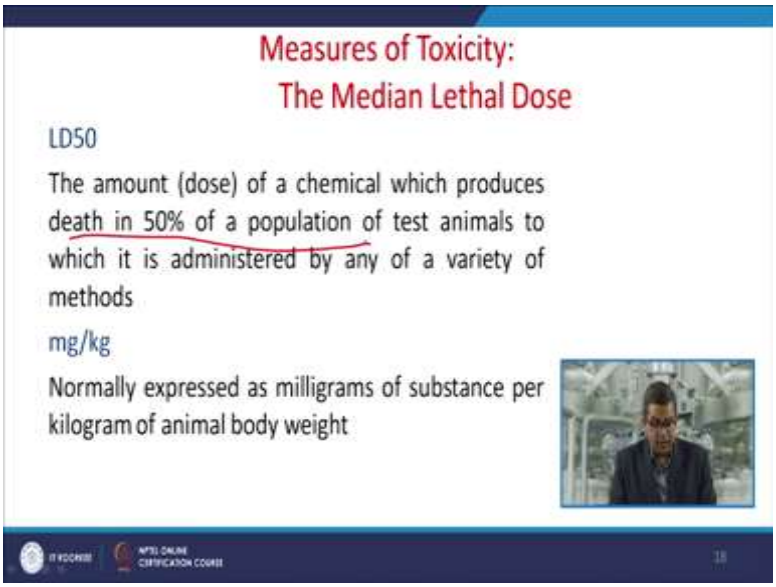
You must find out the dose limit values, and these dose limit values are termed in terms of 3 aspects; EDf- Effective dose for f percent of population, it has reversible response. TDf- Toxic doses for f percentage of population, usually undesirable responses that is irreversible. LDf- Lethal dose for f percentage of population. Now before we go ahead, let me tell you one thing that EDf is reversible and sometimes if you are working and toxic released is most favourable condition because this is the effective dose of percentage of population, this reflects the average effect. So this is the irreversible response because based on your response, your body system, your body may reverse this particular effect of toxic substance, these TDf and LDf, usually they are the undesirable one.

(Refer Slide Time: 17:31)



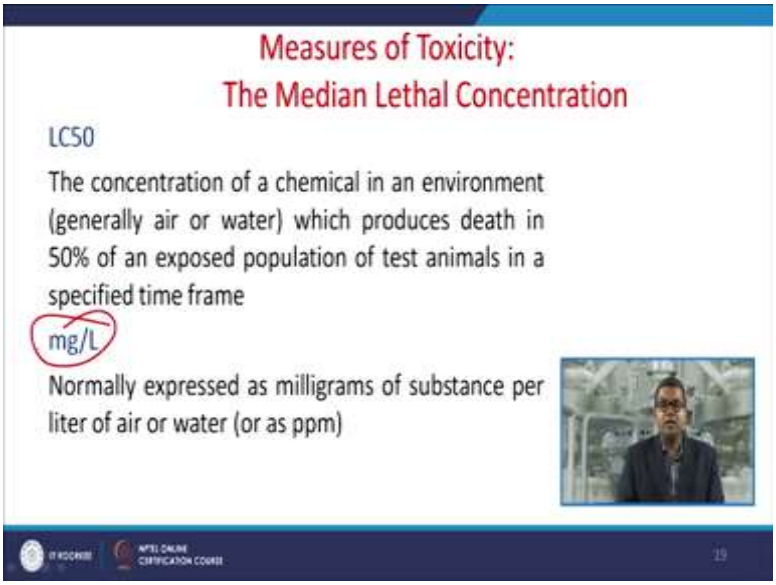
There are certain susceptibility and variability and these are certain parameters; you are young or old it depends because your body structure depends on how old you are! If you are young then based on your immunity, based on other body structure you may overcome the effect of toxic. Male or female, individual variability based on the lifestyle, if your physic is good then definitely you can overcome those problems, there may be certain genetic differences, some people may have certain hereditary problems, et cetera this is one of the most prominent parameters. There are certain species differences may be African countries, Asian, European countries. so these are the certain theoretical parameters.

(Refer Slide Time: 18:48)



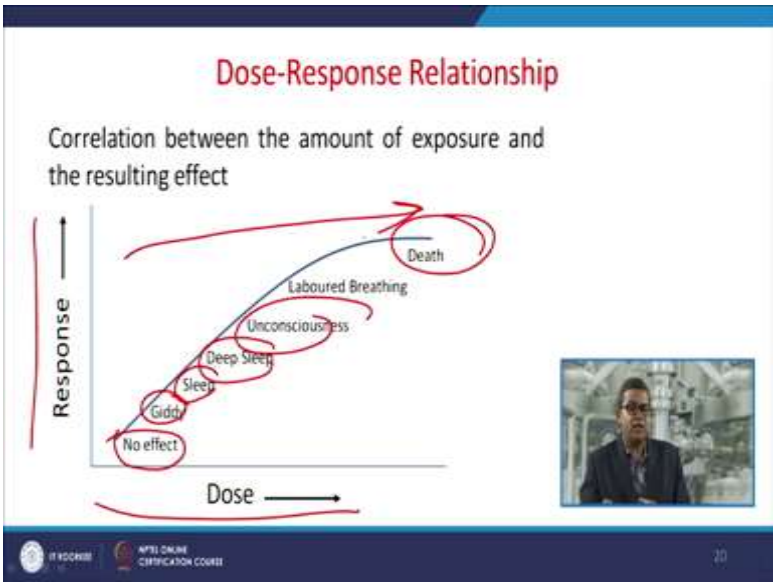
Now before we go into the creation of this dose versus response, we must know that what are the quantitative factors through which we can assess the toxicity, we can assess the problem's gravity. The first thing is that LD50, the amount dose of a chemical which produces the death in 50 percent of population of test animals to which it is administered by any of a variety of methods, usually expressed in terms of milligrams per gram.

(Refer Slide Time: 19:07)



The LC50; concentration of a chemical in an environment generally air or water, which produces death in 50 percent of an exposed population of test animals in a specified time and usually expressed in terms of milligrams per litre.

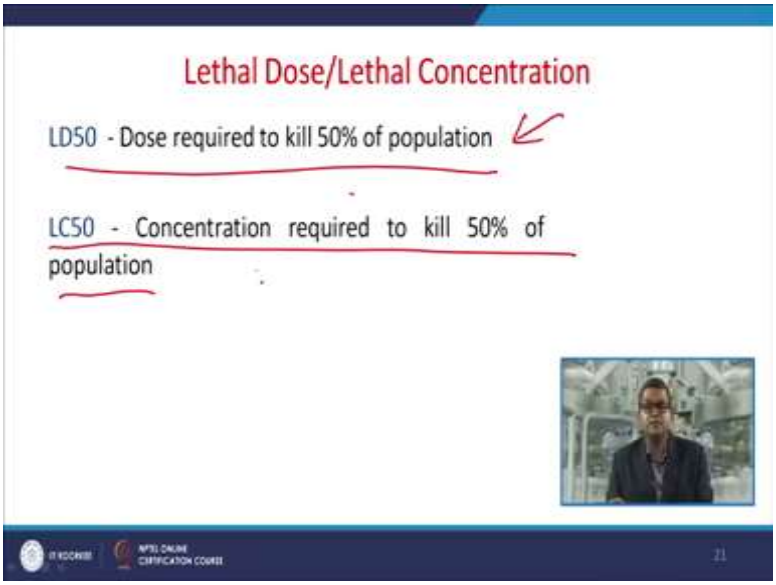
(Refer Slide Time: 19:24)



Now the correlation between the amount of exposure and the resulting effect usually expressed in these terms. It is equally applicable for medicine, equally applicable for toxicological studies. Now if you are having increasing amount of dose, prima facie you may experience no effect then giddy, sleepy, deep sleep, unconsciousness, and even it may lead to the death. So these are the various responses to be recorded, and sometimes fortunately or unfortunately, all

the accidents in the past they gave vital information for the corrective measures in terms of qualitative and quantitative analysis.

(Refer Slide Time: 20:07)



There are certain lethal doses; LD50 dose required to kill 50 percent of population, LC 50 the concentration required to kill 50 percent of the population. So that means you must analyse if you are working in that particular toxic substance environment, you must analyse that how much quantity of dose and how much concentration is lethal because these effects are irreversible in nature.

(Refer Slide Time: 20:43)

Now the question arises that how toxic logical data be obtained? There are various ways enlisted in this particular slide through which you can obtain those data. Maybe with the help of animal toxicological studies, again we need to look into various ethical issues. Accidental human overexposure, maybe in terms of different accidents like Bhopal gas tragedy, the data gave a very crucial information about MIC and other activities. There may be certain controlled exposure of the human volunteers, although certain governments banned these types of test volunteers. Epidemiological studies, they may be descriptive, retrospective, that is usually conventional one, prospective usually it is a cutting edge things.

(Refer Slide Time: 21:40)

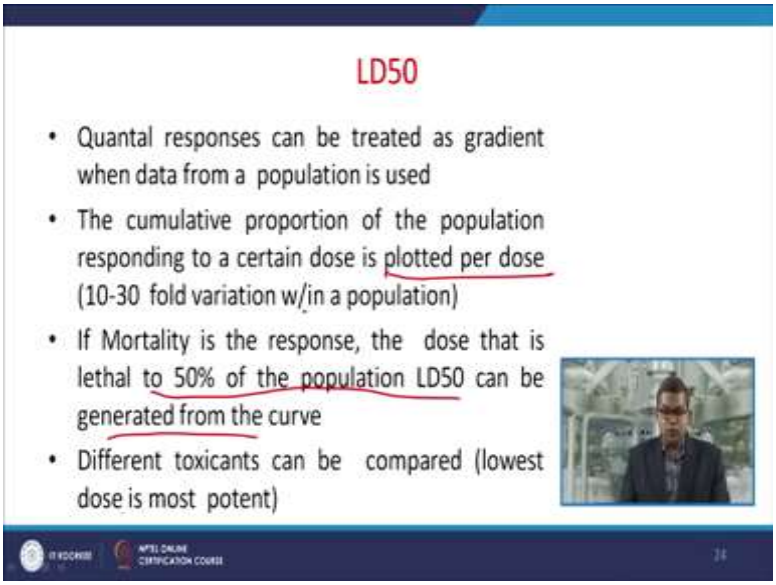
Now again one important aspect is that from where I can get all kind of toxicological information. The prominent source is the material safety data sheet. If you are a chemical company, you are a producer of any chemical then it is mandatory for you to prepare the material safety data sheet not only for the product but also whatever chemicals being used in your site. It gives you prominent information about the identity of the chemical, it gives information about the hazardous ingredients, it gives proper information about the physical and chemical characteristics because in the previous module we have studied that Benzene is available in 2 phases; liquid and vapour phase. So sometimes because based on boiling point, freezing point, et cetera, sometimes if your working condition is designed in such a way that you have to work at elevated temperature then you cannot overlook the importance of this physical and chemical characteristics.

You must have readily available fire and explosion data, this you can have from MSDS that how whether this particular instance is flammable or inflammable and sometimes it may create

explosion or not what is the reactivity because obviously if any particular substance is reactive in nature then definitely your intention would not be in such a way to store in reactive vessel like H2SO4 is highly reactive towards metal, it causes corrosive properties, so obviously you wont to store concentrated H2SO4 in a metal vessel. And similarly the other compounds like sodium, it requires a specific storage attention so that is why it is usually stored in kerosene, you cannot store metal sodium in humid environment.

It is enlisted health hazard data, health hazard data is quite essential not only for the person those who are working in that particular arena but for the nearby people, those who are residing at the outside of that particular plant because it gives information that if that particular component is hazardous then how it can impact to the person those who are working in the nearby area and those who are residing in the nearby area. So you must provide because if this index is on the higher side, definitely you will be more careful. It is just like if you are working in the kitchen then you are more careful towards the LPG Rather than anything else. Then this material safety data sheet, they give you proper information about precautions for safe handling and uses, what kind of control measures need to be adopted in case of any spill over and release, et cetera, we will discuss this material safety data sheet in due course of time.

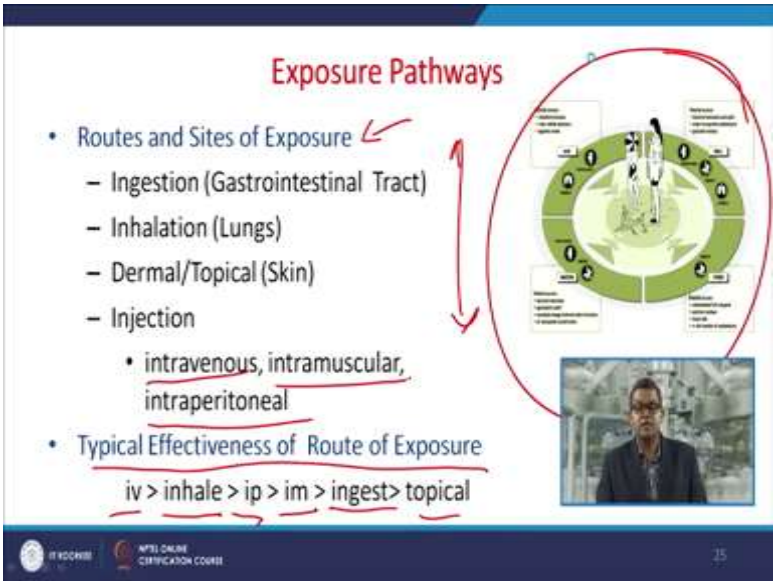
(Refer Slide Time: 25:06)



Now go back to LD50, this is the quantum responses can be treated as a gradient when data from a population is used. The cumulative proportion of the population responding to a certain dose is plotted per dose; 10-30 fold variation with respect to in a population. If mortality is the response, the dose that is lethal to 50 percent of the population and LD50 can be generated from the curve. So it gives you precautionary measure that if this particular dose is lethal for

the person those who are either working within the plant or residing outside the plant. Different toxicant can be compared and the lowest dose is most potent.

(Refer Slide Time: 25:57)

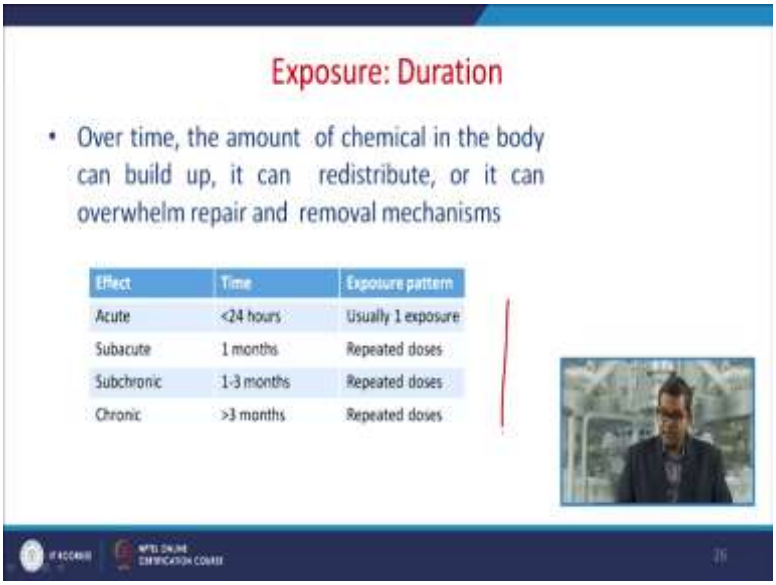


Then you must acquainted that what in exposure pathways. Usually we have discussed in the previous modules, the routes and sites of exposure, these are the 4 routes through which they can enter into the body system. Ingestion is purely based on iv intravenous, intramuscular or intraperitoneal, so typical effectiveness of the route of exposure is

iv > inhale > ip > im > ingest> topical

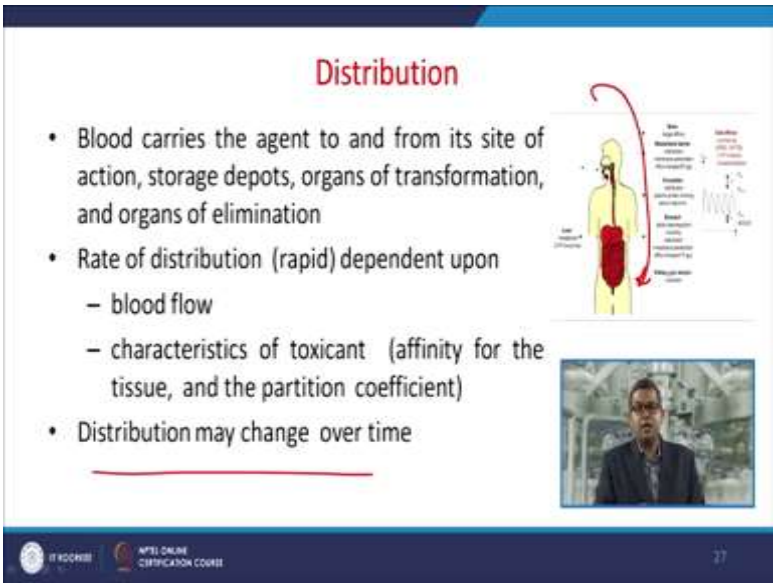
So you must know that what is the exposure pathway.

(Refer Slide Time: 26:35)



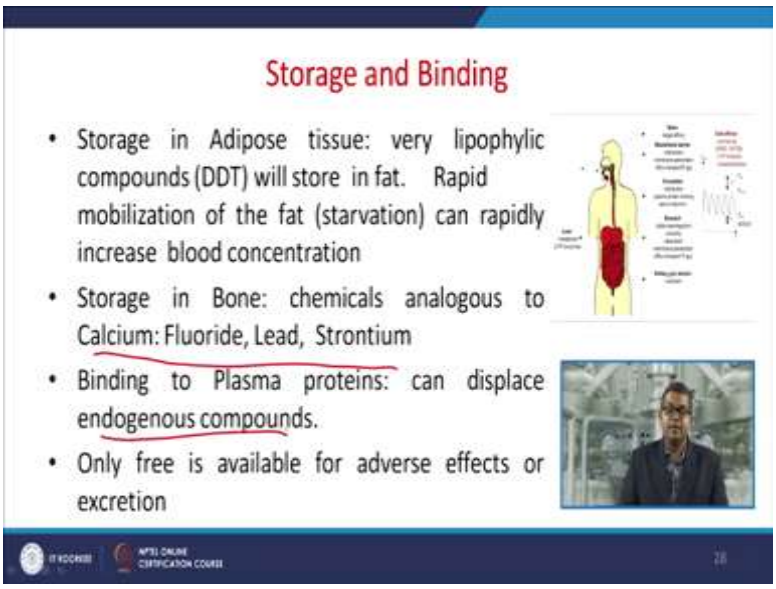
We have already discussed in the previous module about this acute Subchronic effect that if acute is less than 24 hours usually one exposure, sub-acute for one month repeated dose, sub chronic 1 to 3 months repeated doses, chronic greater than 3 months again it is repeated doses.

(Refer Slide Time: 26:59)



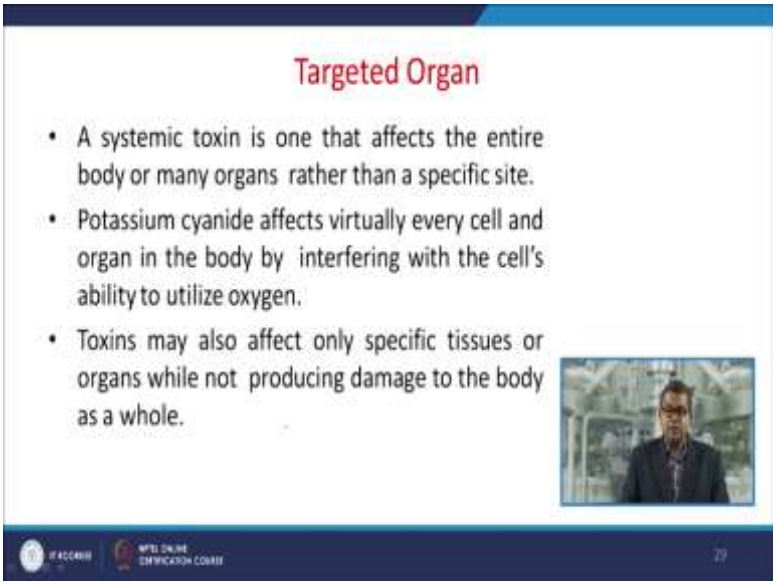
Now you must know that distribution, the blood carries the agent to and from its site of action, storage depots, organs of transformation and organs of elimination. Now rate of distribution depends on usually the blood flow, the characteristics of toxicant, affinity for the tissue and the partition coefficient. And this particular distribution of the things may change over the time, again the dominating factors are age, et cetera.

(Refer Slide Time: 27:36)



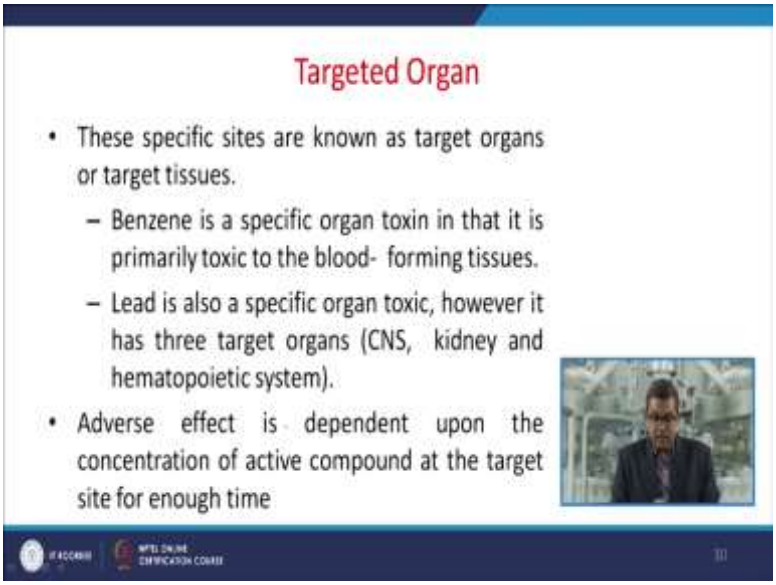
There are certain issues with related to storage and binding. Storage in adipose tissues a very lipophylic compounds like DDT will store in fat and in later part of life may create a problem. Rapid mobilisation of fat can rapidly increase the blood concentration, storage in bone like chemicals analogous to the Calcium: Fluoride, lead and Strontium et cetera because Calcium et cetera Fluoride et cetera they are the part and parcel of your body structure. Binding to plasma proteins; this can displace endogenous compounds. Now only free is available for adverse effects or excretion.

(Refer Slide Time: 28:23)



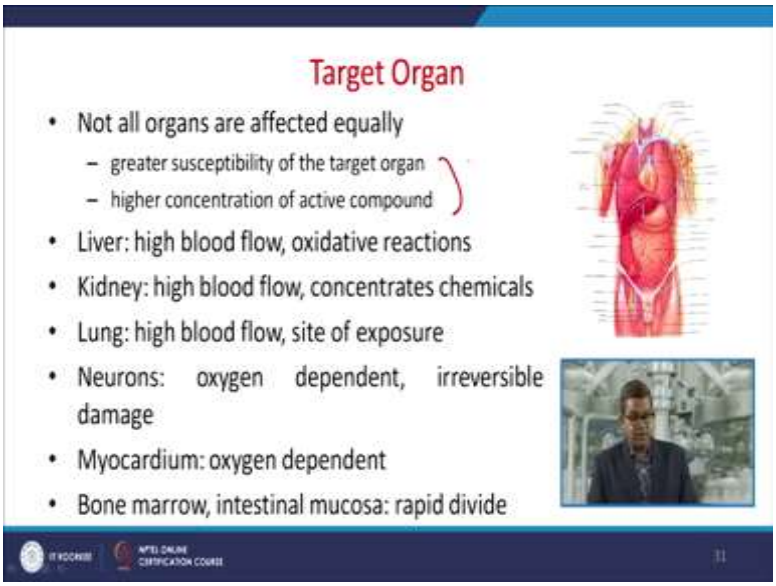
Already we have discussed about the targeted organs, a systematic toxin is one that affects the entire body or many organs rather than the specific site. Potassium cyanide affects virtually every cell and organ in the body by interfering with the self-ability to utilise the oxygen, so usually potential cyanide affects adversely. Toxin may also affect only specific tissues or organs while not producing damage to the body as a whole.

(Refer Slide Time: 29:02)



Now these specific sites are known as target organs or target tissues; benzene is a specific organ toxin in that because toxin is a man-made thing. Toxin in that it is primarily toxic to the blood forming tissues. Lead is also having a specific organ toxic, however it has 3 target organs; kidney, haematopoietic system, and CNS. Adverse effect is dependent upon the concentration of active compound at the target site for enough time.

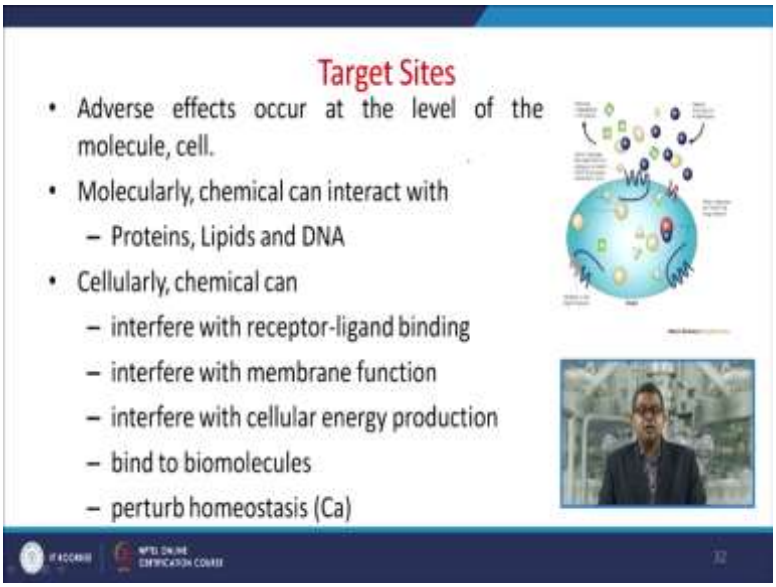
(Refer Slide Time: 29:40)



Now remember, not all organs are affected equally because all toxic substance follow a specific route, and sometimes the route itself tries to detoxify the things. So you must know that the greater susceptibility of the target organ, the higher concentration of active components. So you must be aware about this thing. Liver; usually the high blood flow, oxidative reactions.

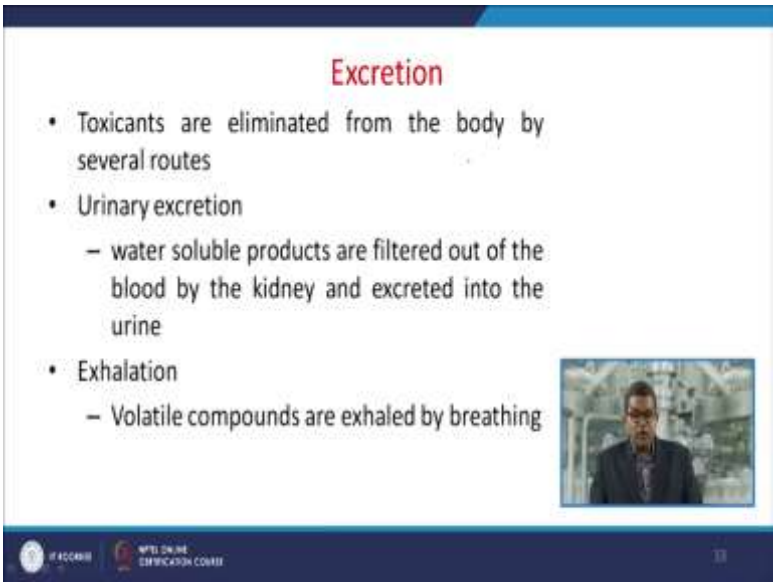
Kidney; the high blood flow and the concentrate chemicals. Lung; high blood flow, site of exposure. Neurons; oxygen dependent, irreversible damage, et cetera. Myocardium; oxygen dependent. Bone marrow, intestinal mucosa; rapidly divided.

(Refer Slide Time: 30:34)



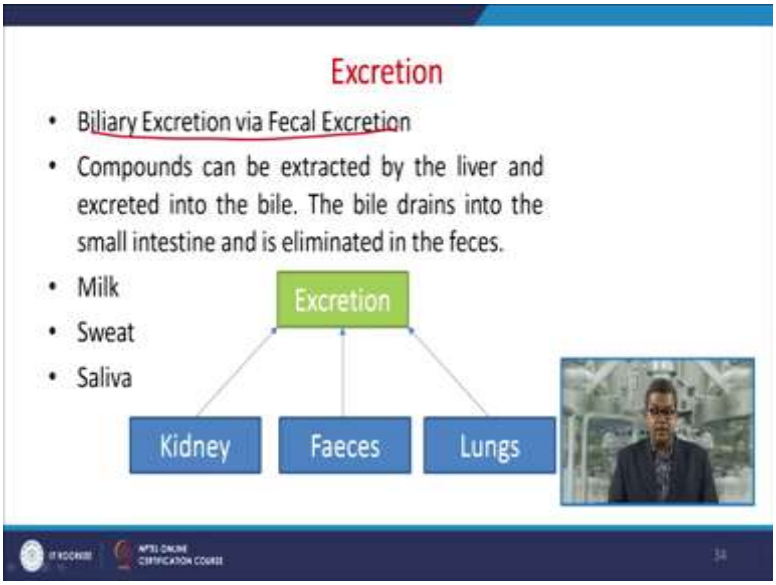
Now adverse effects occurs at the level of molecule or a cell. So molecularly chemical can interact with proteins, lipids and DNA. Cellularly, chemical can interfere with the receptor-ligand binding, interfere with the membrane function, interfere the cellular energy production, bind to biomolecules, perturbed with the homeostasis.

(Refer Slide Time: 31:00)



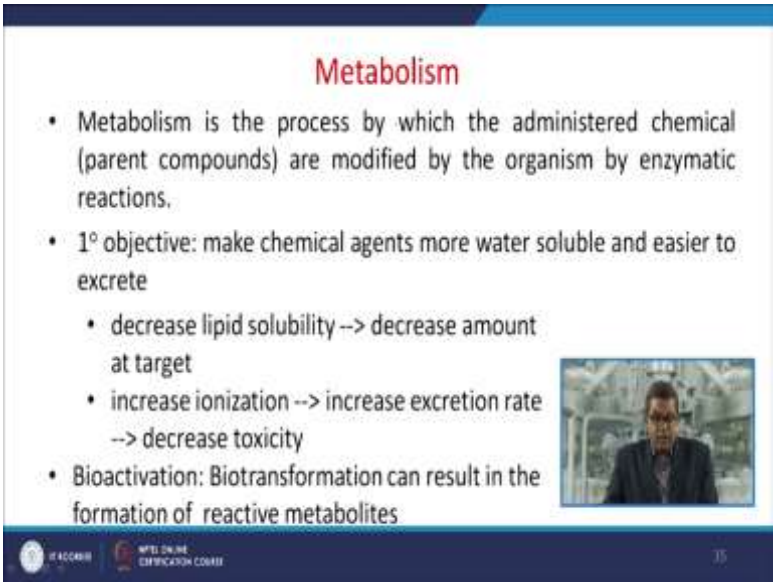
Now once these types of things being analysed, then we should analyse the excretion aspect. The toxicants are usually eliminated from the body by several routes; urinary excretion we have discussed this thing in the previous module, water soluble products are filtered out of the body by kidney and excreted into the urine. Exhalation; volatile compounds are exhaled by the breathing.

(Refer Slide Time: 31:30)



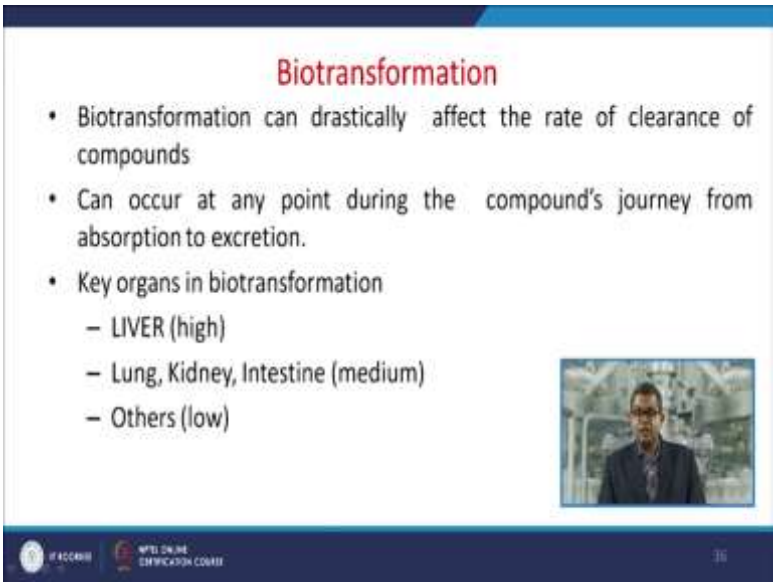
Now usually this excretion route is a Biliaral excretion via fecal excretion, compounds can be extracted by the Liver excreted into the bile and this bile drains into the small intestine and eliminated into the feces.

(Refer Slide Time: 31:49)



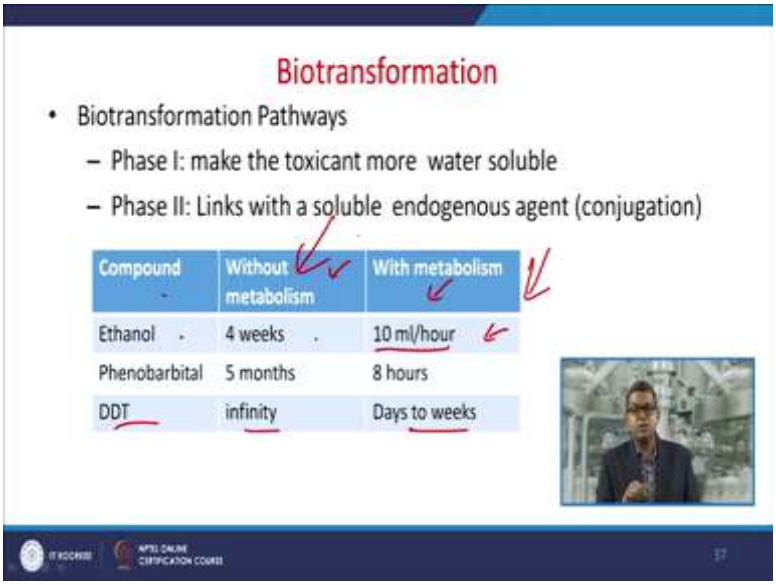
Metabolism, usually metabolism is the process by which the administered chemical that is the parent compound are modified by the organisms by enzymatic reactions. One degree objective is to make the chemical agents more water soluble and easier to excrete; decrease the lipid solubility, decrease amount at target, increase ionisation by increasing excretion rate or decrease the toxicity. Bio-activation; usually biotransformation can result in the formation of reactive metabolites.

(Refer Slide Time: 32:28)



This can drastically affect the rate of clearance of compounds, can occur at any point during the compounds journey from absorption to excretion. The key organs in the biotransformation are Liver, Liver plays a very vital role or you can say among all available organs Liver plays the highest role. The lung, kidney, intestine, they are you can say having medium role, and others which we will discuss in due course of time have a very low contribution towards the biotransformation.

(Refer Slide Time: 33:08)



Usually we have to know that, what are the biotransformation pathways. The phase 1; is to make the toxicants more water-soluble. Phase 2; that is links with soluble endogenous agents like conjugation, et cetera. Now you can see in this particular table that various compounds without metabolism and with metabolism how much the biotransformation affects. Ethanol, 4 weeks without metabolism, and with metabolism 10 ml in an hour. DDT infinity, and days to week, so it all depends that with metabolism and without metabolism what is the response towards the chemical.

So in this particular module we have studied about the various aspects of dose verses response, different parameters, how we can go ahead with the qualitative as well as quantitative analysis because these are the integral parts. In the subsequent module we will study that what are the chemical parameters and what is the individual susceptibility towards those parameters while creating the dose verses response, thank you.