CHEMICAL EXPOSURES: EFFECTS ON HEALTH

Exposure to chemicals is an everyday occurrence. We encounter chemicals in the food we eat, the water we drink, and the air we breathe. All chemicals are toxic at sufficiently high doses. This toxicity may involve damage to tissues, disruption of organ function, developmental defects, illness, or death. The toxic effects of a particular chemical can vary greatly depending upon a variety of factors such as the quantity to which a person has been exposed, the duration and frequency of the exposure, the sensitivity of the exposed individual, and the route through which the chemical enters the body. Thus, if we want to determine the risk of a chemical exposure, it is not sufficient to know that the chemical is present in some particular location. We must also consider the potential for exposure and the specific factors that influence whether toxic effects will occur.

This fact sheet covers the primary factors that determine the risk involved in a chemical exposure. It also describes the general kinds of health effects that may result, with specific descriptions of carcinogenic, developmental, reproductive, and mutagenic effects.

How does the duration of exposure affect toxicity?

Exposure to toxic chemicals can be described as acute or chronic, based on its duration. *Acute exposure* is defined as a single exposure or multiple exposures to a chemical within a short time period, usually less than a day. *Chronic exposure* is one that persists over a long period of time. The exposure, which may be continuous or intermittent, can last for days, months, or even years.

The relationship between dose (how much) and time (how often and for how long) is a major determinant of the effects of chemicals. Acute and chronic exposures to the same dose of a chemical do not necessarily produce the same health effects. A dose of a chemical which is highly toxic when received acutely can be non-toxic or even beneficial when it is received chronically, spread out over a long period of time. For example, ingestion of 1 gram of arsenic at one time would probably be fatal, but ingestion of the same total amount over a period of many years would probably have little effect and may be considered a required nutrient. The opposite is also true. A chemical that is acutely non-toxic may be toxic when received chronically. These effects are related to the ability of the body to detoxify chemicals.

Often our bodies can tolerate small doses of toxic chemicals because the chemicals can be metabolized or excreted from the system. In larger doses, or over long periods of time, however, these chemicals may be able to accumulate in parts of the body where they can do substantial damage.

What are the critical factors that influence toxicity?

The degree of toxicity of a chemical is dependent on a number of factors in addition to exposure duration and frequency. One important factor is the route or pathway of exposure (see Fact Sheet on Routes of Exposure to Environmental Chemicals). Another factor is the combination of different chemicals to which a person is exposed. In combination, two or more chemicals may modify each other's actions or the responses of individuals who are exposed to them. A person need not be exposed to different chemicals at the same point in time for interactive effects to occur. Interactive effects can be additive, synergistic, or neutral.

CRITICAL FACTORS INFLUENCING TOXICITY

- **Potency of chemical**
- **Route of exposure**
- **Dose, frequency, and duration of exposure**
- **Also: Age, sex, nutritional and immunologic status, genetics, general health status, and other environmental exposures**

In addition, a number of individual characteristics, including age, sex, nutritional and immunologic status, genetic characteristics and state of health, all influence the individual's susceptibility to the effects of toxic chemicals. Two individuals exposed to the same dose of a toxic chemical may exhibit quite different reactions, for example, allergic reactions.

A person's state of health is another important factor determining his or her response to toxicants. Individuals with health problems, such as lung diseases (e.g., asthma, emphysema) or kidney disease are more likely to be affected by chemicals that cause damage to these particular target organs.

For some chemical exposures, age clearly affects toxicity. Young children and adults often have different sensitivities to the same chemical. Some substances, such as boric acid and the pesticide parathion, appear to be more toxic to children than adults. Similarly, certain toxicants have differential effects on males and females.

Individual susceptibility may explain why a given dose of a chemical causes different degrees of effects among individuals. Some people who smoke develop lung cancer, but others do not. Differences in susceptibility may be due to genetic variations. Recent research in immunology is also yielding clues about why some individuals are more susceptible than others.

What kind of health effects result from exposure to a toxic chemical?

The health effects that result from exposure to a toxic chemical are classified as being either acute or chronic, based on *how quickly* they appear and *how long* they last. These acute or chronic effects are not the same as acute or chronic exposures. A single, acute exposure may result in long-term (chronic) health effects.

Acute health effects develop rapidly after contact with a chemical. Symptoms are relatively short in duration, lasting from a few minutes to a few days. Some examples of exposures and resulting acute effects include:

- Exposure to ammonia—irritation of the eyes, nose, and throat, difficulty in breathing, and nausea
- Exposure to benzene—decreased alertness, headache, and sleepiness
- Exposure to formaldehyde—irritation of the eyes, nose, throat, and skin.

Chronic health effects are long-term or on-going. They can result from either acute or chronic exposure to a toxic chemical. Sometimes the chronic symptoms that result from these exposures evolve gradually. There is often a long latent period or time lag between a person's initial exposure to a toxic chemical and the appearance of disease symptoms. For example, it can take 20 to 30 years or longer for a person who is exposed to asbestos to develop lung cancer.

Chronic symptoms persist for long periods of time. Some examples of exposures and potential chronic health effects include:

- Chronic exposure to benzene which can lead to leukemia (this is a chronic toxic effect with a relatively short latency compared to other forms of cancer)
- Acute exposure to caustic agents such as lye which can cause permanent scarring of exposed tissues
- Chronic exposure to asbestos which can lead to the lung disease asbestosis and to lung and other cancers.

While chronic health effects are often associated with chronic exposures, this need not be the case. A single, acute exposure to a powerful chemical toxicant may produce enough damage to cause the appearance many years later of chronic health effects such as cancer, nerve damage or, in some instances, even premature death.

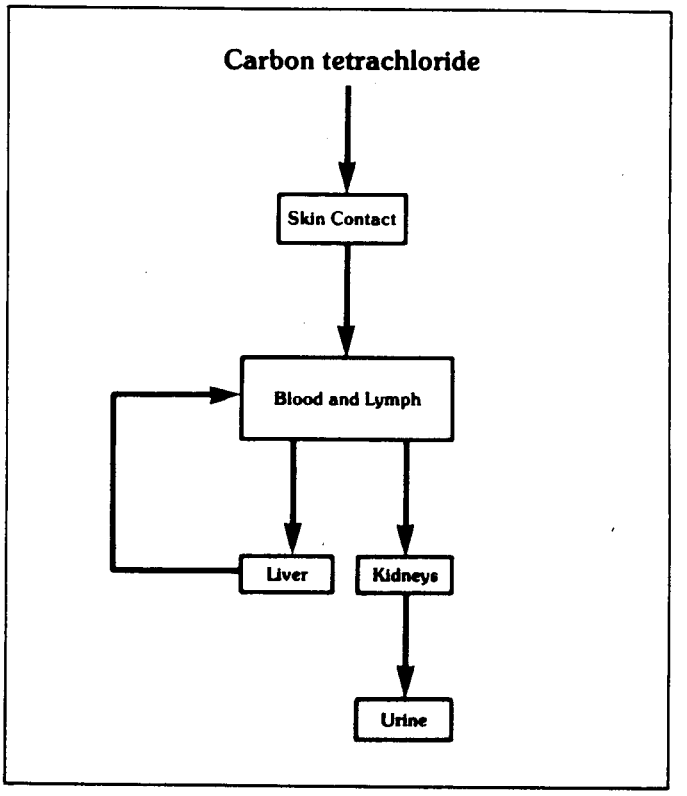
What is the difference between local and systemic health effects?

The damaging effects of a toxic chemical may be described as local or systemic.

An injury is described as *local* if it occurs in the region of the body where the toxic chemical first makes contact. Local effects can occur:

- On the skin or eyes when there is direct contact with the chemical
- In the lungs and other parts of the respiratory tract when toxic vapors, gases, or aerosols are inhaled
- In the digestive tract when toxic chemicals are ingested.

A *systemic* injury is one that occurs after a toxicant has passed into the body to a site distant from its entry point. Once a chemical has crossed certain barriers such as the skin, or the wall of the gastrointestinal tract, it enters the blood and can access various organs or systems of the body. Thus, a chemical such as carbon tetrachloride, which is commonly used as a dry cleaning solvent, makes its first contact with the skin where it causes minor irritation. It can then pass into the blood, and move on to cause systemic damage in the liver and the kidneys, as shown in the diagram below.



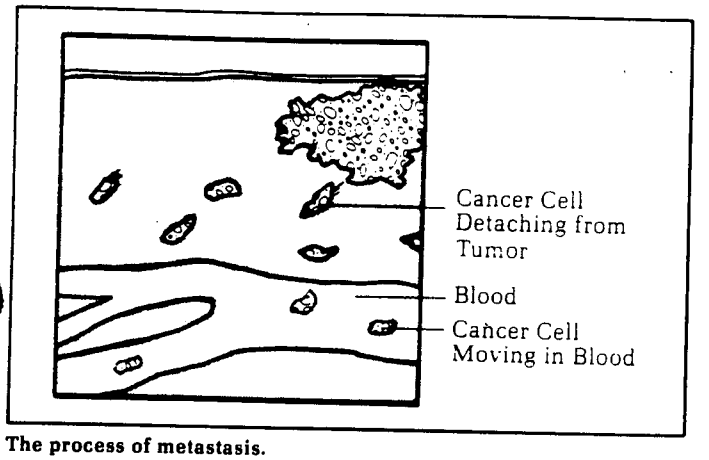
Pathway of carbon tetrachloride after it makes skin contact.

While chemicals can cause injury to any part of the body, their effects have been broadly grouped into categories according to their site of action and method of toxic damage. This half of the fact sheet will cover four important kinds of toxic effects : carcinogenic, developmental, reproductive, and mutagenic.

CARCINOGENIC EFFECTS

What is a carcinogen?

Anything that has the ability to cause cancer may be described as a carcinogen. Carcinogens cause body cells to grow in an abnormal way, resulting in the formation of a malignant mass or tumor, which invades surrounding tissues as it grows. Cells may break off from the tumor and spread to other parts of the body (metastasize), forming new tumors. A cancerous liver cell, for example, can eventually produce cancerous tumors in the lungs.



The process of metastasis.

Where are carcinogens found?

Our daily activities bring us into regular contact with a number of definite or suspected chemical carcinogens. Some are found in the food we eat; some are released into the air by motor vehicles, factories, and other sources of pollutants; and some occur naturally in molds, fungus, rocks, and soil. We are also frequently exposed to some nonchemical carcinogens, such as radiation from the medical use of x-rays, from sunlight, or in naturally occurring radon that is released from the ground and rocks beneath our homes; and we are exposed to biological carcinogens that are found in certain viruses and molds, such as aflatoxins in peanuts and grains.

The fact that we are all exposed to carcinogens, however, does not mean that we will all automatically develop cancer. Many genetic, physiologic, immunologic, nutritional, and lifestyle factors can influence the development of cancer.

In addition, it is important to realize that of the approximately 65,000 chemicals in use, only about 30 are known to be human carcinogens. While many chemicals cause other toxic effects, non-carcinogens do not cause cancer, even at high doses. There are even some antioxidants such as ascorbic acid (vitamin C) that may help prevent the occurrence of cancer.

Is the risk of cancer increased when there is exposure to more than one carcinogen?

Studies suggest that exposure to more than one kind of carcinogen can sometimes result in an interactive effect, leading to an increased risk of cancer. This interactive effect may be *additive*, with the effects of each chemical simply adding together. It may also be *synergistic*, where interacting chemicals produce an effect which is greater than the sum of individual chemical effects. One example of synergism is seen with tobacco smoking. While cigarette smoking alone greatly increases the risk of lung cancer, the risk is further increased in smokers who are exposed to asbestos or radon.

How do carcinogens work?

While the precise mechanism of activity for chemical carcinogens is unknown, there are a number of theories that have been proposed to explain it. One commonly accepted concept classifies carcinogens as initiators and promoters. *Initiators* attack healthy cells and initiate damage, causing changes in the DNA or genetic material of the cell. While the initiated cells may be damaged and vulnerable, they do not necessarily develop into tumors. Instead they become dormant and await further insult. The presence of a second kind of agent, called a *promoter*, enables the initiated cells to grow and become malignant.

How do cancer cells differ from normal cells?

All of the cells of our body have the ability to divide and reproduce themselves. After reaching their normal adult size, the cells do one of three things:

- They become *static cells*, losing their ability to divide. This is true of most muscle and nerve cells. Any loss of these cells cannot be replaced.
- They become *expanding cells*, which stop dividing but have the capacity to switch on and divide again if part of the tissue is removed. For example, if part of the liver is lost through disease or injury, new cells will grow to replace it. Once the liver has returned to its normal size, however, the cells will stop dividing.

- They become *renewing cells*, which continuously divide to replace cells lost on a daily basis. This is true of skin and blood cells. Old cells constantly die and are replaced by new ones.

Normal cells become cancer cells when they are altered by carcinogens. One alteration might involve a turning off of the signal which tells the cells when to stop dividing. Thus, cells in the liver that would normally stop dividing when the organ reached the normal size would keep on dividing, producing tumors.

Cancer cells lose their attachment to the tissues where they form. In contrast, normal cells adhere. In some tissues, normal cells are actually fused to one another; in other tissues, the cells are embedded in a substance (matrix) which holds them in place. In cancerous growths, cells are not held together well and may thus be shed or break loose from the original tumors, enabling them to disseminate and produce metastases in other parts of the body.

Known Human Carcinogens

The following is a list of substances and technological or manufacturing processes that are known to be carcinogenic along with examples of ways that people can be exposed to these carcinogens.

Agent	Exposure
4-Aminobiphenyl	Antioxidant in rubber Manufacture of dyes
Analgesic mixtures containing phenacetin	Drug
Arsenic and certain arsenic compounds	Pesticides, manufacture of glass and ceramics, smelting of metal ores, food and drinking water
Asbestos	Manufacture of asbestos-containing materials, insulation, brake linings
Auramine	Manufacture of dyes
Azathioprine	Drug
Benzene	Manufacture of chemicals, and plastics, paints and adhesives, gasoline fumes
Benzidine	Manufacture of dyes
N,N-bis (2-chloroethyl)-2-napthylamine (chlornaphazine)	Drug
Bis(chloromethyl) ether and technical grade chloromethyl methyl ether	Manufacture of chemicals and plastics
1,4-Butanediol dimethylsulfonate (myleran)	Drug (chemotherapy)
Certain combined chemotherapy for lymphomas (treatment typically comprised of procarbazine, vincristine, prednisone, and nitrogen mustard)	Chemotherapy
Chlorambucil	Drug
Chromium and certain chromium compounds	Manufacture of metal alloys and protective coating on metals, paint, food, and drinking water
Coke oven emissions	Manufacture of coke
Conjugated estrogens	Drug
Cyclophosphamide	Drug
Diethylstilbestrol	Drug
Hematite	Mining of iron ore
Isopropyl alcohol	Manufacture of isopropyl alcohol
Melphalan	Drug
Methoxsalen with ultraviolet A-therapy (PUVA)	Drug
Mustard gas	Chemical warfare agent
2-Naphthylamine	Research purposes
Nickel	Refining of nickel and nickel compounds
Rubber	Manufacture of rubber
Soots, tars, and mineral oils	Manufacture of coal tar and creosote, crude mineral oils and cutting oils, shale oils
Thorium dioxide	X-ray imaging in medical exams; manufacture of ceramics, incandescent lamps, magnesium alloys, nuclear reactors, vacuum tubes
Tobacco and tobacco smoke	Cigarettes, chewing tobacco, snuff
Vinyl chloride	Manufacture of plastics

Source: Public Health Service. U.S. Department of Health and Human Services. *Fourth Annual Report on Carcinogens. 1985 Summary.* NTP 85-002.

How long does it take for cancers to develop?

The process by which a normal cell changes into a cancer cell can sometimes be slow and complicated, often involving numerous exposures to one or more carcinogens. This process can result in a lag or *latency period* between an initial exposure to a carcinogenic chemical and the appearance of cancer. Radiation-induced leukemia, for example, has a latency of approximately five years. Cancer of the lung, on the other hand, may not appear until 30 years after exposure to asbestos. This long delay is one of the reasons why it is so difficult to identify the causes of human cancer. The task is made even more difficult by the fact that many people exposed to a cancer-causing agent never develop any cancer.

Does exposure to carcinogens always cause cancer?

No! A large number of factors affect the probability of developing cancer after exposure to a carcinogen. These factors include the amount, the route, the frequency, and the duration of chemical exposure. Individuals also differ in their tendency to develop cancer. Factors such as genetic background, age, sex, and nutritional and immunologic status all influence an individual's response to carcinogens. There are a number of means by which the human body can defend itself against cancer. For example, the liver plays an important role in breaking down or modifying certain toxic chemicals to reduce their toxicity. Another means is found within the cells, which possess internal repair mechanisms that sometimes are able to restore chemically damaged genetic material (DNA) before irreversible effects occur. In addition, the immune system, which helps to fight off bacterial and viral diseases, also fights off cancers by destroying cancer cells. An immune response may actually prevent the establishment of a cancer or cause the regression of a tumor. While the immune response is not always sufficient to prevent the development and spread of a tumor, new avenues of research suggest that it may soon be possible to harness some of the body's own immune responses in order to fight certain types of cancer. The body is often assisted in the defenses by chemical agents (e.g., anti-oxidants), which help to prevent the occurrence of cancer.

What can be done by an individual to prevent cancer?

In recent years tremendous progress has been made in detecting factors, including environmental factors, that increase the risk of cancer. To the extent that exposure to environmental factors can be controlled, the risk of cancer may be reduced. Overall, chemical exposures should be minimized whenever possible. For example, people can greatly reduce the risk of getting lung cancer by not smoking. People can also reduce cancer risk by handling household products such as cleaning fluids, solvents, and pesticides, with caution and according to label instructions.

DEVELOPMENTAL EFFECTS

Each year, approximately 200,000 babies with birth defects are born in this country. While most birth defects result from unknown causes, it has been estimated that at least 3 percent may be attributed to parental exposure to chemicals or drugs. These chemicals cause *developmental effects* in a number of different ways. They may directly damage the developing fetus, or cause mutations in the germ cells (sperm and eggs) of the parents. Germ cell mutations may then be expressed in the offspring, as functional or structural defects, altered growth, altered behavior, or premature death.

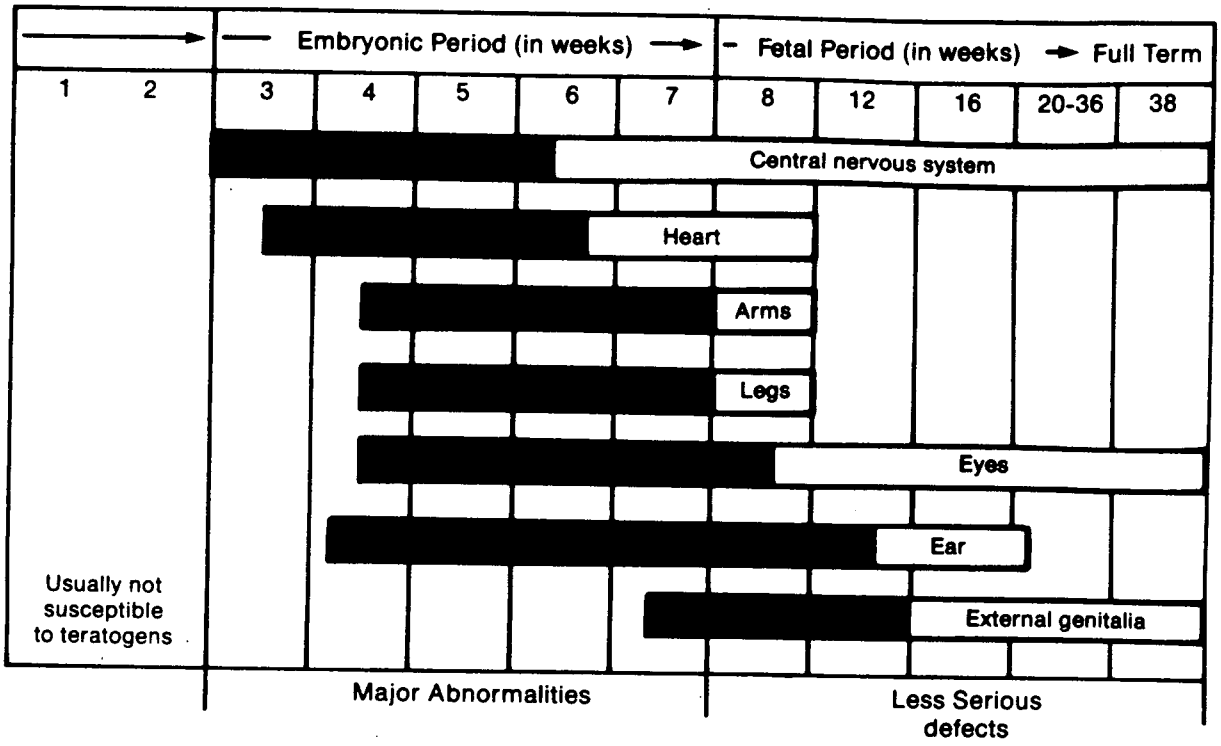
Some chemicals also may cause *reproductive effects*, exerting their toxicity on the reproductive systems of the parents. These effects result in decreased fertility or reproductive capacity.

Toxicants that affect the reproductive system can be quite selective. Chemicals that cause no injury to a parent can create considerable problems for an unborn child. Damage to the genetic material in the sperm and egg can be passed on to future generations.

What is a teratogen?

A teratogen is an agent that causes a physical defect in a fetus during the period between conception and final organ system development. Exposure to a teratogen can interrupt the natural process of fetal organ formation and result in a variety of serious deformities in the newborn child. Teratogenic health effects include heart defects, deformed limbs, and incomplete formation of the gastrointestinal tract.

While some chemical or viral agents can injure both the mother and the fetus, the nature of effects in each may be quite different. The rubella (German measles) virus is



Periods of human development for some major organs. Dark bars show periods of high sensitivity to teratogens.

an example of one such agent, which usually causes only mild fever and rashes in a pregnant woman. However, if a rubella infection occurs during the first three months of pregnancy, the child may be born with serious problems such as congenital heart disease, cataracts, deafness, and mental retardation.

When are teratogens most dangerous to the fetus?

Exposure to teratogenic chemicals is generally most dangerous during the first trimester (first 3 months) of pregnancy, when organ formation is underway. At that time, women often do not know they are pregnant. It is therefore prudent for women of childbearing age to exercise care about exposure to potential teratogens.

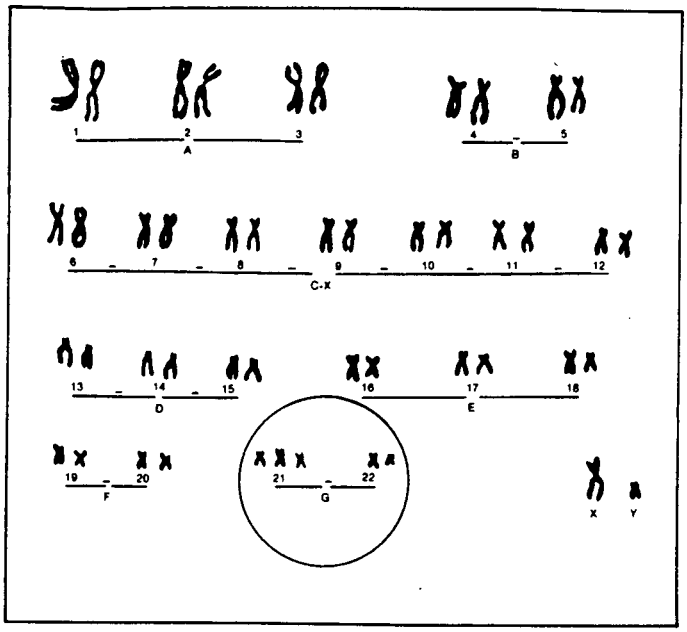
Between the embryo's 3rd and 7th weeks of life, the central nervous system (the brain and the spinal cord), heart, limbs, eyes, and ears are in the process of developing. Chemical exposures during this critical period of organ formation may result in serious birth defects.

By the 3rd month of life, many embryonic organ systems are quite well developed. Teratogenic exposures that occur after this time usually result in less serious defects, such as minor malformations of organs and limbs.

Mutagenic Effects

Mutagenic health effects are the result of chemicals that change the chemical structure of genetic material (DNA) located in the cell nucleus. Genes, the basic units of inheritance, are submicroscopic entities located at various areas on the chromosomes that determine specific traits such as hair and eye color, height, and so on.

Since DNA is "read" to provide information that is critical to cell function and proliferation, mutations may cause a misreading that leads to cell damage, cell death,



or cancer. Damage may take several forms: alteration in the chemical composition of DNA; change in the physical structure of DNA; or addition, deletion, or aberration of chromosomes, of which humans have 23 pairs.

If a mutation occurs in developing sex cells (germinal cells), it may be inherited. Mutations in any other cells (somatic cells) are not inherited. This is very important for the individual and his or her offspring.

Example of an additional chromosome (three instead of two) in Group 21. This is also the specific aberration for Down's Syndrome.

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