Environmental Health Perspectives
Vol. 43, pp. 61-69, 1982

Approaches to Assessing Host Resistance

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There is increasing evidence that chronic, subclinical exposure to certain environmental pollutants may upset immune responsiveness and alter susceptibility of animals to infectious agents. Environmental chemicals or drugs may affect diverse aspects of the immune system, leading to immunosuppression, immunopotentiation, hypersensitivity or perturbed innate host resistance. A variety of infectious models is available that involves relatively well defined target organs and host defense mechanisms; for example, infections with encephalomyocarditis virus, *Herpesvirus simplex, Listeria monocytogenes, Streptococcus pneumoniae, Escherichia coli* or *Plasmodium berghei*. Important variables in infectious models used to assess immunotoxicity include species and strain of animal used, their age and sex, the route of exposure, and dose of the chemical. No one infectious model has yet emerged as a routine screening tool to detect and assess the subtle effects that may occur in immune responses when animals are exposed to doses of environmental pollutants that cause no adverse effect at a gross level. The selection of useful test systems is complicated because it is difficult to measure the effects of chronic, subclinical exposure to chemicals and sublethal challenges of microorganisms.

Introduction

Chronic, subclinical exposure to certain environmental pollutants or drugs may perturb immune responsiveness and alter susceptibility of animals to infectious agents. Environmental chemicals or drugs may affect diverse aspects of the immune system, leading to immunosuppression, immunopotentiation, perturbed innate host resistance and hypersensitivity. A variety of experimental methods are being developed and evaluated in order to assess changes in host resistance following exposure to chemicals. Particular aspects of the vast array of cellular products and cell types involved in immunity can be examined selectively in appropriate models for monitoring host resistance in whole animals. Many of the complexities attendant to the effects of chemicals on immunologic processes, however, are unresolved. It is timely, therefore, to ask whether infectious models can be used routinely to assess immunotoxicity, what their reliability is, and whether they have utility in predicting human risk.

There is evidence that exposure to environmental pollutants causes alterations in various immune responses. Our colleagues have shown, for example, that polychlorinated biphenyls, chloroform and trichloroethylene administered orally to mice for 90 days lead to immunosuppression of some immune responses (*1-4*). In addition, Vos (*5*) and Koller (*6*) have reviewed some results with other chemicals. There is considerable difficulty in interpreting data from different laboratories however. This complexity arises in large part from the rapid proliferation of information and methodology in the field of immunology. Moreover, the protocols used to measure immune functions and the methods for calculating and reporting data may be quite dissimilar for different laboratories. In order to resolve this dilemma, it is necessary to develop a battery of standard assays that can be reproducibly used in different laboratories. Other reasons for inconsistency in results stem from the differences

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Table 1. Important variables in assessing host resistance.

Variable	Routine screening	In-depth study
Strain	One strain	Many strains
Sex	One sex	Both sexes
Age	Young adult	Weanling to aged
Exposure period	Subchronic – 14 days	Subchronic – 90 days
Exposure route	Intraperitoneal	Several routes
Exposure relative to challenge	Pre- and post-challenge	Only before or only after challenge

in animals used (species, strain), in sex, in age (neonatal, weanling, young adult, adult, aged) and finally differences in exposure to the chemical under study (administration before, during or both before and during challenge) (Table 1). In an in-depth study, it may be necessary to use a number of strains because of genetically determined differences. Male and female animals may vary in their handling of a chemical. Weanling or aged animals may be more susceptible to immunotoxicologic effects because such animals are somewhat immunodeficient. Long exposure periods may be necessary because definitive organ site toxicity may not be manifested within a shorter period, such as 14 days. Exposure by inhalation, oral administration or dermal contact may be a more appropriate model for assessing the effects of environmental exposure than intraperitoneal administration.

Effects of Chemicals on Infectious Organisms in Animals

A growing number of reports on adverse effects of environmental chemicals on host resistance to various infections in animals have appeared during the past decade. Some of these are summarized in Table 2. Virus infections, especially with encephalomyocarditis virus, have been the most studied. Interpretation of results from studies using infectious models is even more difficult than those using immunologic assays. Several species as well as different strains of animals have been used, in addition to male and female animals, different ages, different routes of exposure to the chemical (parenteral, oral), and different timing regimens (acute, chronic). These variables have also been confounded by using a variety of infectious agents, for which the pathogenesis and host resistance parameters have been fully established in only a few instances.

We have previously shown that treatment intraperitoneally with some immunomodulators changes host resistance to *Herpesvirus simplex* locally but has no effect systemically (*34*). Similar differences have been observed recently between local and systemic effects in mice fed a high fat diet and given immunomodulator intraperitoneally before Listeria infection. The liver and its macrophages proved to be the target most adversely affected by the high fat diet, while the fixed macrophages in the peritoneal cavity were normally activated after immunomodulator treatment (Campbell and Loria, unpublished results). These data emphasize the importance of separating local from systemic effects, and the necessity of using microbial infections for which the pathogenesis and immune responses have been well characterized. The standard toxicity parameters of lymphoid organ weight, and hematologic profiles are also important in interpreting any changes in host resistance properly.

Potentially Useful Viral Models

Infection with the picornavirus, encephalomyocarditis virus (EMC), has been used extensively in immunotoxicologic studies. This picornavirus produces a rapid systemic illness in mice, particularly in the heart and brain target organs. Systemic infection by EMC is one of the standard infections used to assess efficacy of antiviral therapy (*35*). Host defense mechanisms involved in recovery from this infection have been extensively documented; they include an early interferon response and induction of systemic neutralizing antibody which is independent of T-lymphocytes in the primary response (*36*, *37*). Studies on depletion of macrophages in infection with another picornavirus, Coxsackievirus, have indicated a role for these cells, possibly in an antibody-dependent cell-mediated cytotoxicity (ADCC) reaction which would amplify the viral specific antibody (*36*). Resistance to this virus is not markedly age related, but there are differences between the sexes in some mouse strains (*38*). Genetic resistance has not been as extensively studied as for some other virus infections. The primary importance of antibody in resistance to another picorna-

Table 2. Microbial infections used to assess changes in host resistance upon exposure of animals to environmental chemicals.

Microorganisms	Chemical	Animal	Reference
Viruses			
Herpesviruses			
Pseudorabies virus	Arsenicals	Mice	(*7*)
	TCDD	Mice, C57BL/6Jth	(*8*)
Herpesvirus simplex	Cannabis	Mice, BALB/c	(*9*)
	PCB	Mice, Swiss ICR	(*10*)
Enteroviruses			
Duck hepatitis virus	Dieldrin	Mallards	(*11*)
	DDT	Mallards	(*12*)
	PCB	Mallards	(*13*)
Encephalomyocarditis virus	Toximul MP88 and Atlox 3409 emulsifiers, DDT	Mice, Swiss ICR	(*14-17*)
	Arsenicals	Mice	(*7*)
	Cobalt sufate	Mice	(*18*)
	Cadmium, mercury, lead nickel	Mice, CD-1	(*19*)
	Methylmercury	Mice, Swiss-Webster	(*20*)
	Lead	Mice, Swiss-Webster	(*21*)
Arboviruses			
St. Louis encephalitis	Arsenicals	Mice	(*7*)
Eastern encephalitis virus	Arsenicals	Mice	(*7*)
Langat virus	Lead	Mice	(*22*)
Myxoviruses			
Influenza virus	Sulfur dioxide	Mice, Swiss-Webster	(*23*)
Retroviruses			
Moloney leukemia virus	PCB	Mice, BALB/c	(*24*)
Rauscher leukemia virus	Arsenicals	Mice	(*7*)
	Methylmercury	Mice, BALB/c	(*20*)
	Lead	Mice	(*25*)
Bacteria			
Salmonella bern	TCDD	Mice, C57BL/6Jth	(*8*)
Salmonella typhimurium	Lead	Mice, Swiss-Webster	(*26*)
Listeria monocytogenes	Cannabis	Mice, BALB/c	(*9*)
	PCB	Mice, Swiss ICR	(*10*)
Escherichia coli	Lead	Rat	(*27*)
	Cadmium	Mice	(*27*)
Staphylococcus epidermidis	Lead	Rat	(*27*)
Staphylococcus sp.	Sevin, Dicresyl, Jalan Tilliam, Maneb	Rat	(*28*)
Mycobacterium bovis	Cadmium	Mice, B10-A-2R	(*29*)
Parasites			
Hexamita muris	Cadmium	Mice, Swiss-Webster	(*30*)
Plasmodium berghei	PCB, HCB	Mice, BALB/c	(*31*)
Histomonas meleagridis	*p,p'*-DDT	Chickens	(*32*)
Heligmosomoides polygyrus bakeri	DDT	Mice	(*33*)

virus, echovirus, has also been well documented in patients with agammaglobulinemia (*39*).

Although treatment with an environmental contaminant may reduce various immune responses such as antibody production, it does not inevitably decrease host resistance. In an experiment in which mice were administered trichloromethane by gavage for 14 days, there was no significant change in the delayed hypersensitivity response to sheep erythrocytes nor was there a significant decrease in resistance to EMC virus (Table 3). Serum antibody titers to sheep erythrocytes however were decreased by 63% and 85% with doses of 50 and 250 mg/kg, respectively, in female mice, and by 70% and 79%, respectively, in male mice.

Another infectious agent that may prove useful in immunotoxicity is *Herpesvirus simplex* (HSV). We and others have clearly documented the multifaceted aspects of the immune response that may be involved in resistance to HSV infections (*40, 41*). Sensitization of T-lymphocytes, with subsequent activation of macrophages for antiviral activity, appears to be prominent in host resistance. Whether the same types of macrophages or macrophage functions are involved in antibacterial, antiviral and antitumor resistance is as yet unclear. We have shown that antiviral and antitumor functions of macrophages do not necessarily occur simultaneously (*42*). A role for interferon in the early stages of infection has been documented by

Table 3. Effects of trichloromethane on resistance to encephalomyocarditis (EMC) virus and the immune response to sheep erythrocytes (sRBC).[a]

Treatment, mg/kg	Anti-sRBC titer	Log LD_{50} (95% confidence limits)
None	3401 ± 403	7.2 (6.0–8.0)
Vehicle	5295 ± 808	6.9 (6.2–7.6)
5	4040 ± 318	6.7 (6.1–7.3)
50	1960 ± 234	7.5 (6.5–8.4)
250	820 ± 225	6.4 (6.0–6.9)

[a]Six-week-old female ICR mice were gavaged daily for 14 days with the indicated doses and then challenged intravenously with dilutions of encephalomyocarditis virus, and the LD_{50} determined. Mortality was measured over a 14-day period. Separate groups of mice were immunized with sheep erythrocytes on day 8 of exposure. Serum was collected on day 15 and serum antibody titers were determined. Each anti-sRBC value represents the mean ± standard error of the reciprocal of the titer, based upon 8 mice per group.

showing decreased resistance to HSV in mice treated with anti-interferon serum (*43*). Recently, a role for natural killer (NK) cells and for activated macrophages has been demonstrated for the early stages of infection (*44*). The induction of the T-cell-dependent neutralizing antibody does not appear to be of primary importance in the initial reduction of virus, but may be involved in recovery and altering the latent infection with HSV which often follows primary infection (*45*). Very small amounts of antibody may be amplified tremendously (several magnitudes) by the ADCC reaction (*46*); thus antibody in conjunction with mononuclear phagocytes may also be involved in recovery from primary infection. The presence of neutralizing antibody is sufficient to protect mice from a second challenge with the virus (*47*). HSV infection will thus monitor the adequate functioning of many elements in the immune system: interferon induction, T-lymphocytes, B-lymphocytes, NK cells and macrophages. For these reasons, we believe that HSV infection may be a very sensitive indicator of changes in any aspect of the immune system. We have shown, for example, that depression of either macrophage function or T-lymphocytes markedly reduces resistance to this virus (*40*).

Another potential advantage of this virus infection is that different pathogeneses of infection and induction of immune responses occur with different routes of inoculation (*47, 48*). A local infection resulting in vesicles can be observed clinically after labial or vaginal inoculation of HSV. Moreover, HSV often becomes latent in the sensory ganglia in survivors of infection and the incidence of latency can be markedly altered by changes in the immune responses of the animal (*45*). The latent virus can be reactivated by immunosuppression (*49*). The labial infection is particularly advantageous in all of these respects (local infection, systemic immune responses, latency in the easily accessible trigeminal ganglion, alteration of latency by immune responses and reactivation of latent virus).

There is clear evidence for genetic resistance to HSV. C57BL/6 mice are among the most resistant, and resistance is dominant (*50*). The mechanism of resistance has not been completely defined; Lopez's present hypothesis is that a marrow dependent cell, possibly the NK cell, is involved. We and others have also documented that resistance to HSV also increases considerably with the age of mice (*40*).

Potentially Useful Bacterial Models

Infection with the gram-positive bacterium *Listeria monocytogenes* has been extensively investigated in regard to pathogenesis of infection, and the immune responses that are involved in recovery of animals from infection. From the data reported in the series of elegant studies of Mackaness and colleagues at the Trudeau Institute (*51, 52*), it is now well accepted that recovery from infection depends upon specific sensitization of T-lymphocytes that then activate macrophages for enhanced nonspecific bactericidal activity. Fixed macrophages are also involved in the initial inactivation of the bacterium, while the activation of macrophages occurs within 2-3 days following systemic infection. Resistance to the bacterium can be assessed by mortality, or by bacterial colony counts of the liver and spleen, which are major sites for replication of the bacteria.

The resistance of mice to Listeria can be profoundly altered by the genetic makeup of the animal. For example, the C57BL/6 mouse is resistant, while the A mouse is susceptible (*53*). The mechanism of the genetic resistance is as yet unclear. Bone marrow studies have indicated that resistance is determined by the host rather than by the donor, and that the spleen of the resistant animal is required for expression of the genetic resistance. The current hypothesis is that genetic resistance involves an interaction between macrophages and the microenvironment provided by the resistant genotype (*54*). Despite the complexity of these interactions, Listeria infection provides a reliable model that has been well characterized. The infection primarily assesses competency of T-lymphocytes and macrophages.

Table 4. Effects of cannabinoids on resistance to *Herpesvirus simplex* type 2 (HSV-2) and *Listeria monocytogenes* infections.

Treatment[a]		Decrease in resistance to[b]	
Drug	Dose, mg/kg	Listeria	HSV-2
Vehicle	—	2	6
Δ^9-THC	200	365[c]	96[c]
Marijuana extract	200	88[c]	3
Flumethazone	5	385[c]	10[c]
Cyclophosphamide	200	Not done	260[c]

[a]Mice were inoculated intravenously with dilutions of each microorganism and treated intraperitoneally on days 1 and 2 with the indicated doses of drug. The LD_{50} for HSV-2 was $10^{1.9}$ (95% confidence limits $10^{1.4}$ to $10^{2.4}$), expressed as dilution factors. The LD_{50} for Listeria was $10^{5.2}$ (95% confidence limits $10^{4.8}$ to $10^{5.5}$) colony-forming units. See Morahan et al. (*9*) for complete data.

[b]Decrease in resistance: LD_{50} for untreated group/LD_{50} for treated group.

[c]Significantly different from the untreated group at $p < 0.05$.

Table 5. Effects of polychlorinated biphenyl (PCB) on resistance to *Listeria monocytogenes* or *Herpesvirus simplex* type 2 (HSV-2) infections.

Treatment[a]		Decrease in resistance to[b]	
Drug	Dose, mg/kg	Listeria	HSV-2
PCB vehicle		1	1
PCB	30	3	1
Flumethazone vehicle		2	1
Flumethazone	5	794[c]	20[c]

[a]BALB/c mice were treated for 14 days by gavage with PCB prior to infection or for two days after infection by intraperitoneal administration of flumethazone. Mice were infected intravenously with dilutions of microorganisms. The LD_{50} for HSV-2 was $10^{2.3}$ (dilution factor) and for Listeria the LD_{50} was $10^{5.4}$ colony-forming units. These data were kindly supplied by Munson et al. (*10*).

[b]Decrease in resistance: LD_{50} for untreated group/LD_{50} for treated group.

[c]Significantly different from the untreated control at $p < 0.05$.

We have used both Listeria and HSV infections to assess host response to environmental toxicants and drugs. In one study, the effects of treatment with marijuana extract or with the pure chemical Δ^9-tetrahydrocannabinol (Δ^9-THC) was compared with effects of treatment with the known immunosuppressive alkylating agent, cyclophosphamide, or the steroid flumethazone (Table 4). The standard immunosuppressive regimens markedly decreased resistance to both HSV and Listeria, as did treatment of mice with Δ^9-THC. The course of the Listeria infection was also exacerbated by treatment with marijuana extract but the HSV infection was not. Although there are certain similarities in resistance mechanisms to these two microorganisms, it is clear that there are differences, too (*9*).

In another study, mice were exposed by gavage to polychlorinated biphenyls (Aroclor 1254) daily for 14 days prior to infection with Listeria or HSV-2 (Table 5). Whereas treatment with the known immunosuppressive steroid flumethazone decreased resistance significantly, there was no effect with the polychlorinated biphenyl exposure. This lack of effect on host resistance contrasts with the marked effect observed with this environmental toxicant on standard immune assays. Serum antibody titers to sheep erythrocytes were reduced dose dependently to 20% of control values by 25 mg/kg in male mice and to < 1% of control values in female mice. The delayed hypersensitivity response to sheep erythrocytes was completely abolished in male mice only with the highest dose tested (75 mg/kg); however, a dose of 12.5 mg/kg reduced the delayed hypersensitivity response by 40%. Flumethazone at 5 mg/kg administered subcutaneously on days 1, 2 and 3 after antigen completely suppressed both humoral and cell mediated responses to sheep erythrocytes.

The pathogenesis and immune responses to *Streptococcus pneumoniae* infection have been extensively characterized also. Recovery from infection depends upon the induction of opsonizing antibody, which in conjunction with phagocytic cells, enhances phagocytosis of *S. pneumoniae* and its subsequent intracellular destruction (*55-57*). End points of mortality and measurement of antibody status (by *in vitro* methods or rechallenge of the surviving animals) can be determined. This classic infection thus measures the function of B-lymphocytes and plasma cells to produce the T-cell independent antibody to the pneumococcal polysaccharide, as well as the functional capacity of granulocytic, phagocytic cells.

The gram-negative enteric bacterium *Escherichia coli* is capable of causing a variety of extraintestinal infections in man. Virulence of different strains in intraperitoneal infection of mice correlates well with virulence in natural infection (*58*). Mouse virulence is directly related to survival and multiplication in the peritoneal cavity leading to production of large amounts of endotoxin (*58, 59*). The virulence is correlated with resistance to phagocytosis by both macrophages and polymorphonuclear phagocytes (*58, 59*). Phagocytosis can be enhanced by the presence of opsonins and complement in normal serum or specific antibody to *E. coli* K antigens (*58, 60*). In the later phases of infection, survival should be dependent on the animal's defense against the effects of endotoxin. The

Table 6. Effects of chemicals on resistance to live *Escherichia coli* and purified endotoxin.

Treatment[a]		Decrease in resistance to[b]	
Chemical	Dose, mg/kg	*E. coli* cells	Endotoxin
None	---	1	1
Actinomycin D	0.4	55[c]	266[c]
6-Mercaptopurine	100	55[c]	23[c]
Δ^9-Tetrahydro-cannabinol	150	7[c]	12[c]
Vincristine	1	9[c]	13[c]

[a]Male mice were injected intraperitoneally with drug, live *E. coli* cells or purified gram-negative bacterial endotoxin as indicated. The LD_{50} for actinomycin D was 0.8 mg/kg; for 6-mercaptopurine, 220 mg/kg; for Δ^9-tetrahydrocannabinol, 350 mg/kg; for vincristine, 7 mg/kg; for live *E. coli*, 5.5×10^9 cells/kg; and for purified *E. coli* 0127:B8 (Boivin) endotoxin, 16 mg/kg.

[b]Decrease in resistance: LD_{50} for untreated group/LD_{50} for treated group.

[c]Significantly different from the untreated group at $p < 0.05$.

extraintestinal virulence of a particular *E. coli* strain for mice is influenced by the presence and identity of O and K surface antigens, especially K1 (*60*).

The susceptibility of animals to gram-negative bacteria and their endotoxins can be altered dramatically by a variety of chemicals (*61*). We have studied extensively the enhanced toxicity of gram-negative bacteria or endotoxin in combination with drugs for more than a decade. Drugs that inhibit protein synthesis or ribonucleic acid synthesis render animals unusually susceptible to live *E. coli* or purified endotoxin whereas endotoxin renders animals particularly vulnerable to the adverse effects of drugs that affect deoxyribonucleic acid synthesis, structure or function (*61-63*). Actinomycin D, 6-mercaptopurine, Δ^9-THC and vincristine, for example, at sublethal doses impaired the resistance of mice to challenge with live *E. coli* or purified endotoxin (Table 6). The extent of the decrease in resistance with respect to the two endotoxic sources was similar for each chemical, affirming that endotoxin has some role in the pathogenesis of *E. coli* infections. The interlock among the actions of the host on the drug, of the bacterial pathogen and the test chemical on the host, and of the chemical on the bacteria are especially complex in *E. coli* infections (*62*). Bacterial endotoxin (purified or as gram-negative cells) impairs the activity of the liver mixed function oxidases in treated animals. Several chemicals, for example chlorambucil, are metabolized by these microsomal enzymes (*61-63*). Elevated drug levels resulting from impaired detoxification may retard the growth of live *E. coli* if the test chemical has antimicrobial activity, or they may exacerbate the endotoxic action of the gram-negative bacterium by rendering the host hyperreactive to endotoxin. A number of chemicals affect the integrity of the intestinal mucosa, thereby allowing the "endogenous" gram-negative bacteria to gain access into the circulatory system. These interconnected events may establish a cycle of adverse effects that amplify the interaction between a chemical toxicant and an infectious agent.

Potentially Useful Protozoan Model

Plasmodium berghei, an intracellular sprozoan parasite causing malaria in a variety of rodents, is potentially useful in immunotoxicity assessments (*64*). Mice and rats infected with *p. berghei* have been used extensively as models for examining immunity and host defense mechanisms in malaria and as *in vivo* assays for potential antimalarial drugs. With highly adapted parasites such as Plasmodium, a combination of immunological effector mechanisms of host resistance is well recognized. Ingestion and destruction of antibody-coated or surface-modified Plasmodium and Plasmodium-infected erythrocytes (by phagocytes including macrophages) is thought to be a common effector mechanism (*65*, *66*).

More information is needed however on the molecular changes in parasitized erythrocytes at various stages of Plasmodium development and of the quantitative aspects of antigenic changes (and effects of antibody binding). Inhibition of invasion of erythrocytes by Plasmodium merozoites can be mediated by antibody (*67*). Evidence that T-lymphocytes may also be involved in resistance comes from the observation that mediators of nonspecific resistance, such as BCG organisms, are capable of affecting parasite elimination in some strains of mice while nude mice remain highly susceptible (*68*).

Conclusions

A variety of infectious models are available that involve relatively well defined target organs and host defense mechanisms (Table 7). It appears, however, that no one infectious model has yet emerged as a routine screening tool to detect and assess the subtle toxic effects that may occur in immune responses when animals are exposed to doses of environmental pollutants that cause no adverse effect at a gross level. This conservative judgement of the current state-of-the-art reflects both the sophisticated nature of the cellular and

Table 7. Synopsis of selected infectious models potentially useful in immunotoxicity assessments.

Organism	Target organs after ID or IV inoculation	Host defense mechanisms assessed primarily
Viruses		
Encephalomyocarditis virus	Heart, brain	Interferon production Antibody production by B-cells
Herpesvirus simplex	Local site of infection Central nervous system	Interferon production T-cells Macrophages Natural killer cells Antibody production by B-cells ADCC reaction[a]
Bacteria		
Listeria monocytogenes	Liver, spleen	T-cells Macrophages
Streptococcus pneumoniae	Spleen, liver, lungs, kidneys	Opsonizing (T-cell independent) antibody production by B-cells Antibody dependent phagocytosis and intracellular destruction by granulocytes
Escherichia coli	Peritoneal cavity, liver, spleen	Sensitization to endotoxin Phagocytosis and intracellular destruction by phagocytes Opsonizing antibody production by B-cells Complement
Parasite		
Plasmodium berghei	Erythrocytes, liver, spleen	T-cell dependent antibody production by B-cells Macrophages (ADCC reaction?)

[a]Antibody-dependent cell-mediated cytotoxicity.

molecular interactions operant in host resistance and the experimental reality that the optimum conditions for achieving sensitive and reproducible predictor systems in immunotoxicology have not been adequately defined. The selection of useful test systems will not be achieved easily because it is difficult to work with models concerned with the effects of chronic, subclinical exposure to chemicals. This difficulty is compounded when there is also a need to assess these effects in infection initiated with sublethal challenges of microorganisms.

It is timely to ask whether infectious models should be used routinely to assess immunotoxicity, and which immune dysfunctions cause increased risk to infectious agents or tumors in humans. There is no doubt that immunodeficiency in humans increases risk to infectious diseases. In general terms, patients with B-cell deficiencies are very susceptible to bacterial pathogens but have relatively normal resistance to viral infections. Patients with T-cell deficiencies are very susceptible to fungal, protozoan and viral infections and show increased vulnerability to intracellular bacterial parasites. Patients with phagocytic dysfunction are unusually susceptible to bacterial infections but have relatively normal resistance to viral or protozoan infections. In light of the increasing evidence that low levels of environmental pollutants affect the immune system and impair host resistance to infectious agents (*69*), it is prudent to evaluate the utility of selected infectious models in immunotoxicity assessment.

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